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VIRUSES AND VIRUS-LIKE AGENTS AS CAUSES OF CANCER

A Brief Recounting and Reflection[1, 2]

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During the past dozen years we have all witnessed the impact upon medicine of what Sir Henry Dale has called the second era of research in chemotherapy, as manifested practically in the unparalleled usefulness of the sulfonamides, penicillin, and the newer antimicrobic drugs, and theoretically in the impetus which their discovery has given to new thought and experimentation on the metabolism of parasitic cells, the mechanisms of drugfastness, and the general principles of chemotherapy. Great as these achievements are, they were exceeded, in my opinion, by the attainments of bacteriology in the final quarter of the 19th century. For in that remarkable efflorescence, the genius of Pasteur, the logic of Koch, and the percipience of Lister permeated medicine with incredible rapidity, the immediate consequence being that a host of diseases which had puzzled and plagued mankind for centuries abruptly yielded their causes, and often their cures in addition, as fruits of the new science, while a vastly more important outcome was the fact that man had at long last identified and begun to study the bacterial creatures with which he lives. It was inevitable that these developments should influence thought about cancer.

For cancer was then what tuberculosis, typhoid fever, and anthrax had so lately been—baffling to the mind as well as sinister to the body, amongst the worst of man's afflictions however judged. True, its natural history had been half-disclosed, as much by the clinical and

[1] The Alpha Kappa Kappa Lecture given in Hurd Memorial Hall, The Johns Hopkins Hospital, November 18, 1947.

[2] Recent investigations in the author's laboratory on viruses and virus-like agents in relation to tumors have been supported by the Jane Coffin Childs Memorial Fund for Medical Research.

anatomical studies of Morgagni, Pott, Bichat, John Hunter, Laennec, and their like, as by the histological observations of Johannes Müller, Remak, Virchow, Cohnheim, Ribbert, Waldeyer, Hansemann, Thiersh, and Pianese, to name but a few of that army of workers who had set about exploring the human body cell by cell as soon as the compound microscope had become available. But only the wooliest notions existed then as to the possible causes of cancer, and nothing was known about the disease that weighed very heavily against the supposition that it might be caused by a pathogenic bacterium. Indeed the erroneous but prevailing doctrine of Broussais and Virchow—that cancer is but a form of inflammation—must have made the possibility seem quite near. In any event, many workers acted on it, and some spent their scientific lives isolating from cancer after cancer bacteria of many and diverse sorts, trying with these to reproduce the tumors under controlled conditions in experimental animals. Alas, their results were uniformly negative or unconvincing, and eventually they all had to accept it as a fact that causative bacteria cannot be grown from cancers. And eventually interest waned in the old superstitions about "cancer-houses", "cancer-streets", and "cancer-villages", which had made it seem that cancer was catching and which had got their start from a series of inexact observations and uncritical inferences that must have made Claude Bernard turn his face, the more so since they had originated in France. Things looked gloomy indeed for the hypothesis that cancers may be caused by extraneous pathogenic agents.

But then the filtrable viruses made a discreet entry onto this bustling bacteriological scene, first tobacco mosaic virus in 1892 and then that of hoof and mouth disease in 1898. Reason enough, it seemed to many, and notably to a bold and imaginative Frenchman named Borrel, for further thought about the parasitic hypothesis of cancer causation. For these new agents produced disease even though they could not be seen with the microscope or grown on lifeless media. Did they cause cancer? Far from overlooking the new possibility, Borrel rushed headlong to meet it. "The problem of cancer causation had taken entire possession of his eager, inquiring mind,"—as Oberling tells us in *The Riddle of Cancer*, "and he had examined tumors by the hundreds and from all possible sources, animals, and man, for a specific

microbe. All in vain. Too critical to let himself be carried away with other bacteriologists by inadequate proofs, or to persevere in a line of investigation now so obviously destined to lead nowhere, he conceived the notion that he might be facing the same difficulties that had baffled Pasteur in his search for the cause of rabies. A virus seemed the only plausible solution." In a remarkably percipient essay published in 1903, Borrel pointed to the proliferative character of the initial cellular changes in small pox and molluscum contagiosum, and compared these with cancer (9). His thought has elicited sharp criticism, but the facts upon which it was based have proved sound, and from much subsequent work, notably that of Philibert (43), Rivers (45), and Shope (54, 55), the principle has emerged that viruses can make cells grow as well as cause their death. Upon this principle and another since apprehended—namely that viruses can lie latent in tissues, producing lesions only when provoked into pathogenicity by one or another of a variety of stimuli—recent protagonists of the view that viruses cause cancer have mainly built their arguments (3, 49).

OLDER WORK ON FILTRABLE AGENTS AND TUMORS

It is one thing, however, to recognize the principle that a few viruses can bring about more or less transitory proliferation—the majority being swiftly lethal to their cellular hosts—and quite another thing to ask whether viruses actually cause cancer. Some of the facts that bear upon this question may be cited briefly and chronologically as follows.

In 1902 the observation was reported that a filtrable virus is responsible for fowl pox, and subsequent events have shown that this interesting disease process deserves a more conspicuous place in the history of cancer research than the one into which it has fallen (22). Bollinger, one of the first to study fowl pox histologically, classified it as a tumor, even though it was manifestly infectious; he named it epithelioma contagiosum in 1873 (8), and others since have noted its resemblance to molluscum contagiosum of human beings. Today, however, fowl pox is not thought of as a neoplasm; for it is essentially a self-limited process, necrosis eventually following proliferation in the diseased cells, which mummify and are cast away in due course with complete healing underneath if the host has not died meanwhile from

an associated sepsis.[3] Its importance in the history of cancer research lies in the fact that it was the first tumor-like process that was proved to be caused by a filtrable virus; as such it inevitably influenced the subsequent study of tumors in fowls, which we may next consider.

In 1903, Ellerman and Bang reported that they had been able to transmit leukemias and lymphomas of chickens by means of filtrable agents, and their findings were immediately confirmed by Hirschfeld and Jacoby, and later by Schmeisser (17). The fact that the blood stream was conspicuously invaded in these disease processes coupled with the fact that filtrable agents had been found responsible for them, seemed sufficient reason at the time to rule them out as tumors, and many years elapsed before their neoplastic character became generally recognized (18).

In 1911, Peyton Rous made the significant discovery that a sarcoma of fowls, which he had previously identified as a neoplasm by careful biological and morphological studies, was transmissible by means of a filtrable agent (48). He and his associates soon determined that a number of other sarcomas of fowls would likewise yield filtrable agents of a similar sort, and that each agent would elicit a growth exactly like that from which it had come if brought into contact with normal fowl mesenchyme under appropriate experimental conditions. The findings have been confirmed in laboratories all over the world, and perhaps extended here and there (13, 19). It has become plain that they stand apart and comprise the bulk if not the sum of what we know today about cellular factors that actually cause cancer.

MORE RECENT WORK ON VIRUSES IN RELATION TO CANCER

The findings just mentioned long stood alone as providing evidence that filtrable agents may be present in cancer cells and responsible for their malignancy, for during more than 20 years the repeated attempts of workers everywhere to extract causative viruses from tumors of many sorts in mammals and other species all proved unsuccessful. Lately, however, the picture has acquired more detail.

[3] It is interesting to note in passing that within the past few years the disease, occurring epidemically in wild sooty grouse, has been mistaken for cancer—vide, Journal of Wildlife Management, **4**: 311–312, 1940.

In 1933, Shope made the discovery that the cutaneous papillomas of Western cottontail rabbits are caused by a filtrable virus that will reproduce the growths when rubbed into the scarified skin of other rabbit species, both domestic and wild (55). Rous and Beard next showed that the virus-induced papillomas, though benign, possess certain of the attributes of neoplasms (50), and that the growths in domestic rabbits, after remaining harmless for periods of several months to a year or more, almost regularly become squamous cell carcinomas that metastasize and kill their hosts (51). Rous and Kidd then found that the papilloma virus will call forth in great profusion a variety of carcinomas, as well as papillomas, when brought into contact with tarred epidermis (53), and Rous and Friedewald later showed that carcinomas appear within a few weeks in papillomas exposed to methylcholanthrene more or less constantly from the time of their inception (52). The relationship, however, between the virus, which initiates the benign papillomas, and the cancers, which come later, has proved exceedingly complicated. For while readily recoverable in large amounts from the natural and experimental papillomas of wild cottontail rabbits, the virus is only occasionally demonstrable, and then in comparatively small amounts, in extracts of the papillomas produced with it in domestic rabbits, and it could not be extracted at all from the cancers, as much work showed (56, 27, 21). In this unsatisfactory position, with the essential facts unlearned about the state and functions of the virus in the papilloma and carcinoma cells of wild and domestic rabbits (33), the problem rested for quite some time, though indirect evidence, procured by means of serological and immunological experiments, made it plain that the papilloma virus, in masked or altered form, persisted in the cells of two transplanted cancers that had originated in virus-induced papillomas, and increased in amount as the cancer cells proliferated (34, 29). The inference seemed warranted that the virus, obviously responsible for the initial proliferation of the papilloma cells, likewise impelled the cancer cells with which it remained associated. But quite recently an extraordinary fact has emerged with respect to the relationship between the virus and the cells of the V2 carcinoma (this being the second of the two transplanted cancers mentioned above, the first having been lost early in the course

of transplantation). For having persisted in the V2 carcinoma cells for more than five years and throughout the first 25 successive tumor generations, the antigenic virus has now, after a further interval of five years, disappeared from them; or at any rate it is no longer disclosed in them by serological experiments of the sort that regularly accomplished this before (57). Can it be that the papilloma virus went along with the carcinoma cells merely for the ride, so to speak, playing no very essential part in their malignant activities during its long association with them? This seems not unlikely, for the V2 carcinoma cells are now, in the absence of the virus, precisely what they were in its presence, so far as can be told from their appearance and behavior, while the fact is well known that non-neoplastic viruses may thus ride along in tumors (37, 47, 29, 60). Wholly apart from this new and unexpected development, I have elsewhere indicated reasons for supposing that a constituent of the V2 carcinoma cells other than the papilloma virus may be responsible for their continuing malignancy and may indeed have initiated their malignant transformation (32). More will be said further on about this.

The observations of Lucké, on the etiology of certain renal adenocarcinomas in frogs, broaden the base of our theme. In 1934, he noted that acidophilic intranuclear inclusions are conspicuous in the cells of these tumors and similar to those previously found by Dorothy Russell in the elements of gliomas in human beings (39). Lucké later showed that the frog carcinomas can be produced experimentally by means of a filtrable agent extractable from them (39); the causative agent, however, acts only sporadically and after a long incubation period, and its properties have not been fully defined.

The foregoing review of recent work on viruses in relation to tumors could easily be enlarged by references to scores of additional papers, but it seems doubtful that it would be notably enriched thereby. For the bulk of the papers that might be cited report at most but microscopic extensions of principles already largely understood from previous work, while some are filled with fallacies, and others lack strategic orientation and perspective. By no means are virus-workers immune from Woglom's pointed dictum (64): "—Few investigators seem to realize that cancer research is a discipline requiring some apprentice-

ship, and that not everyone with an inoculating needle and a dozen white mice can plunge in and emerge with a discovery." The recent claims of Taylor, that filtrable cancer-producing agents can be recovered from mammalian tumors grown in developing chick embryos, would seem to merit our attention only in relation to the reports from other laboratories that the essential observations are unverifiable (61). And all of the extensive work with the Shope fibroma may logically be omitted from consideration; for although knowledge about this virus-induced process has added substantially to the principle already referred to that viruses can make cells proliferate, and although the lesion is "tumor-like," as Shope said (54), it is not neoplastic, the nodules produced by the virus being invariably self-limited and composed for the most part of exudative fluid and "sick" fibrocytes that eventually die and are resorbed.

VIRUS-LIKE AGENTS AND CANCER CAUSATION

To think about viruses in relation to cancer would hardly be feasible without taking count to some extent of the vexed problem of what viruses are. Are they parasites, once free-living but now dependent on their cellular hosts—the simplified products of a retrograde evolution, as Green (24), Laidlaw (36), and Burnet (11) have supposed? Or are they non-living protein molecules, perhaps derived initially from the host's own protoplasm, as Stanley's work may indicate (59)? Or may they be microbial midgets of diverse kinds, as a class occupying and perhaps bridging the twilight zone between the living and the dead in nature, as Rivers has imagined (46)? It is not profitable to our theme to do more now than ask these questions, yet it may be helpful to have them before us as we consider certain other agents that may be concerned in the causation of cancer.

The first of the agents that I shall call virus-like and here discuss is that implicated in the causation of cancer of the breast in mice. It has long been known that the females of some breeds of mice are prone to develop cancer of the breast, while those of other lines are virtually free from the disease; and it was of course assumed that this predisposition was inherited by way of the genes until facts proved it otherwise. In 1933 and 1934, it became clear from experiments done independently by the Staff of the Jackson Memorial Laboratory in this country (38)

and by Korteweg in Holland (35) that the tendency to mammary carcinoma is passed along only by way of the mother: if she be of high-cancer stock, her progeny develop breast cancers largely irrespective of their paternal heritage, whereas if her high-cancer strain brother be mated with a low-cancer female, their progeny are usually devoid of the disease. Bittner then showed, in 1936, by means of foster-nursing experiments that this "maternal influence"—obviously "extra-chromasomal"—is carried in the mother's milk (7), and much study has since been made of the distribution, properties, and potentialities of the "milk factor" (2). It manifestly passes from teat to mouth during suckling and increases in amount during its sojourn in successive hosts; and in concert with certain hormonal and constitutional influences, it obviously plays a crucial part in the etiology of one type of mammary adenocarcinoma. Yet, as much work has shown, it is harmless to mice of many strains and to males and castrated females of susceptible lines unless hormonal stimulation is given artificially to them during long periods of time. It seems especially noteworthy that the milk factor has not caused cancer directly under any of the experimental conditions devised thus far. As I have pointed out elsewhere (32), we remain ignorant of whatever part it may play in producing the malignant change that finally comes about in the benign mammary adenomas in mice susceptible to breast cancer, and no evidence exists that it is essential to the continued proliferation of the malignant cells. Furthermore, its physical, chemical, and antigenic properties as defined thus far do not suffice to distinguish it as a virus, the sedimentable constituents of normal tissue cells being comparable to it in the properties deemed significant. Virus-like indeed the milk factor is, when considered broadly, but the fact deserves reiteration that its precise position in the hierarchy of things and its actual part in the pathogenesis of breast cancer in mice remain yet to be ascertained. It may well be a carcinogenic agent—in the sense that under highly specific circumstances it brings about intracellular conditions favorable to the onset of malignancy—but in the end, like the Shope papilloma virus, it may turn out to be an epiphenomenon so far as the continued causation of cancer is concerned.

Finally, we may consider briefly, in relation to the problem of malignancy, two virus-like agents that can be identified by serological means

in tumors. Some years ago, for reasons which I shall not here relate, I was led to ask whether the methods of serology might prove useful as a means of demonstrating in cancer cells the substances that make them such (28). From an extensive series of investigations along these lines, it has become plain that the cells of the Brown-Pearce rabbit carcinoma, a typical transplantable cancer of unknown cause, will regularly yield a distinctive substance which is identifiable by serological means. This material has not been detectable in extracts of other rabbit tissues, either normal or neoplastic; in a number of experiments it did not elicit tumors when brought into contact with normal and experimentally altered rabbit tissues, yet upon analysis it proved to have certain physical and chemical properties remarkably similar to those of the viruses—notably a large particle size and weight as determined by ultrafiltration and ultracentrifugation—and other properties which suggest that it is probably a protein and perhaps a ribose nucleoprotein (30). The subsequent studies of Claude and others have shown, however, that these physical and chemical properties are likewise shared by particulate components of many normal tissues, though it is clear that the specific constituent of Brown-Pearce tumor cells can be readily distinguished from the particulate components of normal rabbit tissues by serological means (30). Like the filtrable agents responsible for fowl sarcomas, the distinctive constituent of the Brown-Pearce carcinoma cell seems to be associated with, or to concur with, constituents of its malignant host cells that are similar in chemical and serological properties to the cytoplasmic microsomes of normal tissue cells as defined by Claude (14, 30, 31, 32)—an association that may have meaning in view of the time-honored implication that the formed constituents of cytoplasm play important parts in the activities of cells, as for example in determining differentiation and in mediating synthetic activities as well perhaps as in providing active centers for energy metabolism. Recent observations have provided evidence that the distinctive constituent plays an essential part in the proliferative activities of Brown-Pearce carcinoma cells, for it has been shown that the antibody that reacts specifically with the distinctive constituent suppresses the growth of living Brown-Pearce carcinoma cells under a variety of experimental conditions (31). In other serological investigations, facts have been uncovered which indicate that another substance, similar to

that of the Brown-Pearce carcinoma cell yet readily distinguishable from it serologically, is present in the cells of the V2 carcinoma, already mentioned, and absent from benign papilloma cells of the type from which they sprang. The findings considered together have led me recently to inquire (32) whether distinctive constituents such as those associated with Brown-Pearce and V2 carcinoma cells may not be present in the generality of cancer cells and responsible for their continuing malignancy, each type of neoplastic cell having perhaps a special kind of constituent which, by its intracellular activities, determines the particular misbehavior of the cell (autonomy), and which, by crowding out or overgrowing or suppressing the activities of the cell's normal constituents, brings about a degradation of its normal form and functions (anaplasia).

* * *

In medical science, as in fishing, it may be important to have a good backcast if one's forecast isn't to be a mess. Hence I have tried in this small essay to provide perspective as well as intellectual provender for those who may wish to think particularly about the actuating causes of cancer. Although pathetically small in number and permeated through and through by uncertainties, the examples herein cited comprise the essence of what we know today about the intrinsic factors that make cancer cells what they are.[4]

Recently it has become fashionable to suppose that further advances in knowledge about cancer will come largely, if not entirely, from new discoveries in one or another of the fields of intracellular physiology, chief encouragement being derived from prospects in the study of growth as a phenomenon. As a result, a whole host of new workers has begun to think about cancer, and during the past few years its

[4] No consideration need by given to the so-called carcinogenic agents—tar, polycyclic hydrocarbons, x-rays, sunlight, arsenic, butter-yellow, etc.—in this, relation. For while these agents may initiate cancer, it is well known that they like certain of the agents herein described, play no essential part in the continuing and malignant activities of cancer cells. Nor should we be deterred even momentarily by the resounding phrase *somatic mutation* in explanation of cancer, the term representing at present either a supposition inherently untestable by Mendelian methods and one against which formidable theoretical objections can be raised, or a pretentious and misleading label for the unknown, as I have pointed out in another place (32).

causation has been explained theoretically by analogies drawn from a number of rather distant sources. For example, from the hypothesis that plasmagenes are influential in determining the structure and behavior of tissue cells (plasmagenes being hypothetical cytoplasmic entities presumably analogous to nuclear genes, and, like the latter, possessing molecular dimensions as yet undefined), a number of authors have advanced the supposition that aberrant forms of these conjectural entities may be responsible for malignancy (15, 25), while from the conception that mutant plastids cause variegational diseases and viroses in plants, and from the supposition that all tissue cells harbor ultramicroscopic symbionts analogous to the intracellular "bacteroids" of cockroaches, other authors in turn (65, 1) have assumed that anomalous forms of those entities may cause cancer, and still other essayists have put forth related formulations having points of orientation somewhat less discernible. It is indeed interesting that a number of scientists working in different parts of the world on widely various aspects of cellular biology should more or less simultaneously synthesize the view that variations in cytoplasmic entities may be responsible for the permanent, irreversible, and heritable alteration in tissue cells that constitutes cancer. Yet too much emphasis cannot be laid on the point that all of this is mere hypothesis, now jerry-built upon other hypotheses, and comparable perhaps to the first formulations of the somatic mutation hypothesis of cancer causation some thirty years ago; hypothesis it will remain unless altered cellular constituents can be demonstrated in malignant cells and shown to be responsible for their malfunction.

The broadening of the attack on cancer, however, is of course all to the good, for in a problem so vast and intricate who can tell whence the next advance may come? And who can assay the benefits to it of the substantial achievements of cytology and genetics, old and new (63, 10, 41, 26, 62), and of the factual contributions and important implications provided by recent work on a wide variety of cells (6, 58, 44, 12, 5, 23, 4, 16)? And what mightn't it profit the oncologist to know in detail all of what remains yet to be learned about growth and differentiation in normal cells—to comprehend, for example, the minutiae of mitosis, the vital doings of cytoplasmic and nuclear nucleoproteins, and the riddles of protein synthesis, of energy metabolism, and of specialized

cellular functions, not to mention the scores of related problems that immediately come to mind. Yet MacCallum was wise, it seems to me, in putting the section on tumors at the end of his Textbook of Pathology (40), along with this statement: "—We are quite familiar with the effects of every sort of injurious influence in disturbing temporarily the normal growth of tissue, and can formulate general laws for these effects which are found to be always respected. But tumors do not respect them at all. For that reason I have written of tumor growth separately from all the rest of pathology as a thing apart, not to be dealt with according to the laws of reaction of normal tissues." Thinking along the same lines, Foulds, an experimental pathologist, in a detailed and closely-reasoned histological and biological analysis of tumors (20), has written: "It is far from certain that complete knowledge of the forces which control the development and maintenance of normal structure would solve the problems of cancer." Should the point of view be submerged by current coordinations of cancer research?

In striking contrast to all of the factors that work for the good of cells, the viruses are predatory villains, invisible and notoriously subversive, yet dramatic and conspicuous in their effects, their activities as a rule bringing sickness and death to their cellular hosts. The sum of what has been learned about them and about their effects on cells, however, has not been without profit to cellular biology; in quantity and in precision it compares not unfavorably with what can now be marshalled about the nature and effects of other agents—cellular constituents, hormones, organisers, inducers, for example—that comprise and influence the structure and function of normal cells. It is quite conceivable that the viruses may prove increasingly useful as reagents for the study of intracellular processes, both normal and abnormal. Perhaps, indeed, the dim and uncharted lane between intracellular pathology and intracellular physiology can with profit be trod in both directions, becoming in due course a travelled and well-marked highway. Even so, it may prove important to encourage those who seek within the cancer cell for the cause of its enduring malignancy; for therein it surely lurks, and perchance also the means for its control, whereas it may be latent or submerged in non-neoplastic cells, or even absent from them. For all, however, who would learn the ways of cells, the examples herein described, of viruses and virus-like agents in relation to their malignant hosts, may serve as useful guides.

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THERAPEUTIC CONFERENCE
THE TREATMENT OF EPILEPSY

Held in the Hurd Memorial Hall on October 25, 1947

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Dr. A. McGehee Harvey: The subject for discussion today is the management of patients with epilepsy. Until recent years, most of our knowledge developed in a rather empirical fashion. Investigative techniques now available have resulted in an increased interest in this symptom complex, and facts which have a sound experimental background are rapidly accumulating. In view of the intense clinical and experimental activity now going on in this field, it seems appropriate to bring together the pharmacologist, the neurophysiologist, the neurologist, the neurosurgeon, and the psychiatrist in a discussion of the present state of our knowledge and the future trends in research.

The first speaker will be Dr. Butler, who will tell us about anti-convulsive drugs.

Dr. Thomas C. Butler: This discussion will be concerned with only one aspect of the management of epilepsy, the suppression of the seizures by means of drugs. It will be devoted principally to the problems of detecting antiepileptic activity in the laboratory.

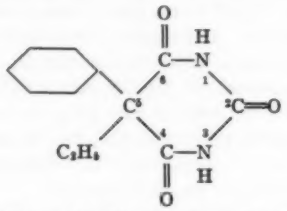
The bromides and phenobarbital, the principal drugs in use ten years ago, had both found their way into the clinical treatment of epilepsy without the benefit of any preliminary laboratory investigation directed toward a search for that particular type of activity. Potassium bromide, the first really effective agent against epilepsy, was introduced in 1857, and it owed its trial to theoretical reasoning that proved to be fallacious. Sir Charles Locock had read the report of a German who had taken potassium bromide himself and had noted as one of the effects of the drug the development of sexual impotence. Locock, thinking that the drug might have some specific effect on sexual functions, tried it on some female patients who had attacks of what he termed "hysterical epilepsy" in connection with the menses. He found the drug efficacious and later extended its use to other types of epilepsy. Even though the reasoning that led to the trial of potassium bromide may have been scarcely more valid than that which had suggested the use of hundreds of other remedies during the preceding centuries, potassium bromide happened to differ from its predecessors in being a really effective antiepileptic agent, and it was not long before it was so recognized.

The effectiveness of phenobarbital was disclosed as the result of clinical trial of every hypnotic agent that became available. After the first report of its use in epilepsy in 1912, it gradually began to be realized that phenobarbital, in comparison with other hypnotics even in the barbituric acid group, had antiepileptic activity out of proportion to its hypnotic activity. The accumulating experience

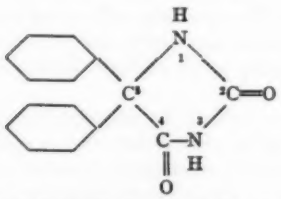
with hypnotic agents in epilepsy was giving increasing evidence that antiepileptic activity was not a simple manifestation of general anesthetic activity.

The drugs of greatest interest that have been introduced during the last few years have received their clinical trial as a result of laboratory tests designed to uncover antiepileptic activity. This is not to say that the tests we have are known to be completely reliable guides. Nevertheless, whether for entirely valid reasons

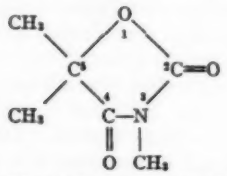
FIG. 1. STRUCTURAL FORMULAS OF SEVERAL ANTICONVULSANT DRUGS



5-ethyl-5-phenyl barbituric acid, or phenobarbital



5,5-diphenylhydantoin, or dilantin



3,5,5-trimethyloxazolidine-2,4-dione, or trimethadione ("tridione")

or not, they have led to the trial of drugs that have proved valuable therapeutically and which promise to give a better insight into the nature of antiepileptic activity.

The study of the so-called experimental epilepsies is by no means new. There are many ways of causing animals to undergo convulsive seizures which bear more or less resemblance to the attacks in the epileptic patient. On account of the ease of producing them, the most thoroughly studied laboratory seizures are those produced by convulsant poisons and those produced by electrical stimulation of the brain.

Fritsch and Hitzig, who in 1870 first discovered the effects of electrical stimulation of the motor cortex, also described the convulsions that could be produced by strong stimulation. They were able to duplicate the development of a typical Jacksonian seizure, and so confirmed Hughlings Jackson's earlier speculations as to the nature of these attacks. It was immediately realized that this means of producing epileptiform seizures furnished an opportunity of testing drugs to be used in human therapy. Hitzig studied the effects of ether and morphine on cortical excitability. The same method was used by a few other investigators of that period to study the effects of some of the anesthetics and hypnotics then in use. However, the number of promising drugs available at that time was so small that this represented no progress in the search for antiepileptic drugs.

At the beginning of this century groups in France and Switzerland were experimenting on the convulsive effects of the passage of interrupted direct current or of alternating current through the intact head. This method was used as early as 1904 for testing several well known drugs, but the first application to the testing of a large series of compounds, with the view of uncovering antiepileptic activity, was the work of Merritt and Putnam in 1938. Merritt and Putnam used cats, with one electrode in the mouth and one on the occiput. They found that the familiar drugs produced effects on the convulsive threshold correlating with their known effects in human epilepsy. A number of compounds, not previously tested as antiepileptics, were found to be active in raising the threshold.

As a result of this experimental work, one of these compounds has had a very thorough clinical investigation. This is 5,5-diphenylhydantoin. Hydantoin is a compound structurally related to barbituric acid, and the 5,5-disubstituted hydantoins resemble the corresponding barbituric acids rather closely in their pharmacological properties. This particular compound, like a number of other hydantoins and barbituric acids, does not produce smooth anesthesia in animals. It produces a picture of combined excitation and depression, and in low doses actually appears purely convulsant. It affords no protection against convulsant drugs such as metrazol. According to the ideas then prevalent as to the nature of antiepileptic drugs, diphenylhydantoin is a drug that would not have been expected to be active and doubtless would never have had a clinical trial had it not been tested in this way. The tests in man soon showed that the drug was, in fact, a highly effective agent in suppressing grand mal seizures, that it produced less hypnosis than phenobarbital, and that it differed qualitatively from phenobarbital in its action in that it was effective in types of epilepsy where phenobarbital was ineffective.

The success of the method of Merritt and Putnam in disclosing such a valuable and interesting drug as diphenylhydantoin naturally has led to the very widespread testing of drugs by similar procedures. Comparison of the results of various investigators leaves one with a picture of confusion and conflict. While some are in essential agreement with Merritt and Putnam, others find that diphenylhydantoin does not raise the convulsive threshold at all, or has less effect than phenobarbital. This conflict apparently stems from the fact that almost every worker has used different placements of electrodes, different durations of shock, different

types of current, and, probably most important, different species of animals. There is some reason to believe that in different species, or with the passage of current through different paths, the convulsive discharges may arise in different foci. Experiments have been reported which suggest that diphenylhydantoin influences only those convulsions arising in the cortex. Further efforts to elucidate the site and nature of the action of known antiepileptics would seem profitable in order to put the testing of new agents on a sounder basis.

During the last four years, considerable study has been devoted to a drug which has been found to differ from the older antiepileptic agents both in laboratory and clinical tests. This drug is trimethadione. It is a derivative of oxazolidinedione, a compound which also resembles barbituric acid in structure. Derivatives of oxazolidinedione in which the 5-position is substituted with two alkyl groups have hypnotic activity resembling that of the corresponding barbituric acids. This particular compound is hypnotic, but one of the least active hypnotics among the oxazolidinediones that have been studied. It has been found active in raising the convulsive threshold in electroshock, even by those techniques that fail to show an action of diphenylhydantoin. Unlike diphenylhydantoin, but like phenobarbital and other barbituric acids, it is an effective antagonist of metrazol and certain other convulsant drugs. The surprising finding on clinical trial was that the drug, while failing to suppress grand mal attacks, was quite effective in petit mal.

From the knowledge now at hand, it would be difficult to make any final appraisal of the value of laboratory methods at our disposal for studying antiepileptic activity. By electrical stimulation it is possible to duplicate quite closely those seizures arising in the motor cortex, not in respect to the initiating cause but in respect to the spread of the neuronal discharge. Because of the difference in the initiating processes, it is not *a priori* obvious that all drugs will behave similarly in the two conditions. However, the electrically produced convulsion, at least in some animal species and in the hands of some investigators, has shown drug response in very good correlation with grand mal epilepsy in man. Those clinical seizures arising from discharge in other parts of the brain than the motor cortex are more difficult to reproduce and study in the laboratory. Trimethadione has been responsible for a revival of interest in the antagonism to convulsant drugs. The relationship of activity of this type to activity in petit mal epilepsy is by no means clear. The metrazol convulsion, although obviously not duplicating at all closely a petit mal seizure, may have some points of similarity. Of what value it will be in uncovering activity against petit mal is problematical.

These three drugs, phenobarbital, diphenylhydantoin, and trimethadione, have had sufficiently thorough clinical investigation to establish that they have qualitatively different types of action. It is to be hoped that intensive laboratory study of these drugs may clarify the basis of their differences and indicate the means by which superior drugs may be searched for in the future. However, it is obviously unsafe to base any very far-reaching generalizations on experience with such a small number of drugs. Any tentative conclusions must be tested eventually by careful clinical studies of a much larger number of appropriately selected drugs.

It may be worthwhile to speculate briefly as to the future in the field of antiepileptic drugs. There is certainly reason to desire better drugs than those we have now. Diphenylhydantoin and trimethadione have brought with them therapeutic benefits not furnished by phenobarbital, but they have also brought toxic effects not produced by phenobarbital. There is no reason to believe that these particular compounds are the best members of their own chemical types, or that antiepileptic activity is confined to structures closely resembling these. So it does not seem unreasonable to hope that the present drugs will be improved upon, certainly in respect to toxicity if not in respect to effectiveness.

Dr. Harvey: Dr. Magladery will now take up the management of epilepsy from the viewpoint of the clinician.

Dr. John Magladery: This morning we are going to discuss the management of the epileptic patient. It is a subject replete with many therapeutic facets, any one of which might be an ample topic for such a discussion. For obvious reasons, therefore, we shall attempt to keep this presentation on a very general level.

It is well to take stock before proceeding to a consideration of measures which may be adopted to combat or modify any pathological process or disease entity. One must be familiar with the natural course of the abnormality, recognize its more common manifestations, appreciate the significance (when present) of certain features, understand what assistance may be obtained from special investigations and, perhaps more important, realize the limitations of such. Finally, and this is especially true of today's subject, one must be well aware of the dual relationship of the abnormality to the patient as a human being—the emotional responses evoked by the disturbance, and the possible modifications of the abnormality by the emotional state of the individual.

It has become apparent that one must now limit the term epilepsy in some way. Clearly, there are many apparently normal individuals showing some degree of alteration in electro-encephalographic pattern, of an intermittent character, and that this "epileptic tendency", as it is sometimes called, shows strong hereditary features. Perhaps this represents a tendency on the part of such individuals to develop clinical seizures in the face of alterations in blood flow, cellular chemistry, intracranial pressure relationships, and so on, which would not lead to such per se in other people. The cause of such tendency is of course completely unknown and will presumably remain so until we have some knowledge of the basis of the different neural circuits contributing to normal rhythmic cortical activity, factors influencing facilitation and inhibition, suppression, and so on. For various reasons, however, and often for no apparent reason, these individuals may develop clinical seizures. This tendency to recurrent excessive discharges when it produces clinical attacks or fits, we term epilepsy, and we are thrust back on a clinical understanding of the features of this symptom.

Here it becomes difficult. The clinical aspects of epilepsy are so many and so diverse that any formulation based on symptoms is hardly feasible. There are

discrepancies in any rigid criteria even as to what constitutes a fit. Prolongations of aura or post-ictal states may even detract from the comparatively sound clinical guides of sudden onset, brief duration (a few minutes at the most), and recurring habit.

The possibility of establishing a working etiological classification of epilepsy seems more likely now than ever before. The roles of hypoglycemia in some seizures, overventilation in others, hydration, the influence of minor cortical structural changes, in addition to more gross abnormalities, have all reached established acceptance. This is so true that there seem reasonable grounds for the view that all epilepsies are really "*symptomatic*". Nevertheless, we are currently forced for tutorial reasons to confess our ignorance in the large majority of cases and lump them together as "*cryptogenic*", or of obscure origin. There is nothing distinctive or mysterious in the latter group to separate it from the symptomatic epilepsies—either may show any of the descriptive subgroups which have clinical similarities or are sometimes (as stressed by Gibbs and Lennox) accompanied by rather distinctive electro-encephalographic patterns: Jacksonian, grand mal, petit mal, psychomotor, akinetic, etc. I do not propose going into descriptions of these today. Our important problem in distinction *must be*—is this epilepsy initiated or favored by an infection, structural lesion, or metabolic change which lends itself to correction by present-day means or, on the other hand, can our therapy be directed solely to the modification of the underlying cerebral dysrhythmia and of the patient as a human being? In other words, is this symptomatic or cryptogenic epilepsy?

The differentiation, of course, devolves on an understanding of the clinical features of these various factors (and time does not permit discussion of these factors) but it can be furthered in certain ways. An important one lies in the age of the patient. Another lies in the attention to focal symptoms and signs—the latter absent, and the former uncommon, in cryptogenic epilepsy. Finally, further assistance can be obtained from special measures such as skull and chest x-rays, blood serological tests, urinalyses, and fasting blood sugars. Some groups would puncture and do encephalograms on all epileptics, and there is much to be said for that practice. This can be reserved, however, for those with other suggestions of intracranial space-occupying or focal disease *only* by accepting the responsibility of frequent examination of the patient. It must be remembered that in several large series, 40–50% of all patients with seizures secondary to tumors had them as initial symptoms. Electro-encephalograms used indiscriminately are of very limited value. Patients in the older age groups and those showing focal lesions are important in the search for focal or predominantly localized changes.

The plan of treatment of each epileptic patient must develop in an orderly fashion and be directed towards various factors involved. There is rarely any great need for immediate institution of therapy, and each case merits detailed consideration of these factors before and during treatment. It is not merely a

question of administering certain drugs in fixed dosages to patients, but rather of the institution of a studied long-term care of the individual.

Certain aspects of treatment associated with the various precipitating factors indicated above need only to be mentioned again—the operative treatment of foci associated with space-occupying lesions, trauma, vascular anomalies and the adequate treatment of syphilis—the management, medical or surgical, of hypoglycemia—and so on. Let us rather consider what measures we have for the prevention or modification of the epileptic attacks themselves, be they symptomatic or cryptogenic.

In the first place, attention must be turned to the patient himself. It is uncommon to find epilepsy first showing itself in the face of emotional difficulties or during the course of a psychogenic illness. Yet it is common experience that, once initiated, the frequency and continuance of attacks often depend on the emotional state of the patient. They are more frequent with insecurity and lack of purpose. In some cases, infrequent attacks may be completely controlled by good psychiatric management alone.

The converse is more strikingly evident. Every individual subject to repeated epileptic attacks faces a tremendous hurdle in his attempts at adjustment in society. If these have started early in life there is every possibility that he has been over-protected by his family; has been considered as different, at the very least, by his school fellows; has, in some cases, been deprived of schooling; has repeatedly been the centre of undue interest, either protective or horror-stricken. In adult life, these features are augmented by failure to obtain or hold employment, the barrier of marriage, and so on. It is not surprising, therefore, that personality changes in response to fear, frustration, repeated failure, are common amongst epileptics. Most observers agree that there is nothing specific about the pattern though numerous references to the so-called "epileptic personality" are to be found in the literature. Assistance must often be given then to the individual in his social adjustment, in rehabilitation measures, employment.

Deterioration in cryptogenic epilepsy is a vexing problem. It is unquestionably related in many cases to the psychogenic factors mentioned above; in others to the post-convulsive state associated with frequently-occurring seizures; in others to the too-enthusiastic use of medication. The correction of these influences often leads to a marked improvement. In a few cases unfortunately, and the explanation is not clear, deterioration is progressive and eventually may require institutional care.

It is necessary, for the protection of the patient and others, to place certain restrictions on his activities, on driving a motor car—working in various potentially dangerous occupations—and so on, at least until he has shown himself under perfect control for a long period. This is introduced at this point to stress the fact that these restrictions should be specific and minimal, and their imposition should be made with full cognizance of their emotional value to the patient.

We can pass quickly over general measures in the control of the epileptic at-

tacks. The work of McQuarrie, Temple Fay, and others has emphasized the relation of fluid intake to the frequency of seizures. Marked dehydrative measures do reduce their incidence in large series; excessive fluid intakes lead to an increase in frequency. However, this is far from universally true for any individual case. The best results have been obtained under strict regimes which are difficult to maintain. Perhaps its only therapeutic application lies in some degree of fluid restriction during febrile illnesses in epileptic children, and in instructions to all epileptics about the avoidance of excessive fluids of any sort.

Despite the suggestive improvement of some individuals under ketogenic diets, this is also not very impressive numerically, and again introduces a difficult and strict regime.

One word should be said about alcohol. Some individuals only have seizures during or following alcoholic bouts. All epileptics have inherently one formidable hazard—they are ill-advised from the standpoint of safety, or even the law, to add another hazard.

The foundation of the control of epileptic seizures lies in adequate drug therapy. This means the use of the most effective drug or combination of drugs in sufficient dosage, the avoidance of drug reactions, and finally the exhibition of the material at the time most needed. The choice of drugs has become an important matter and there are several from which to choose. No doubt the list of possibilities will increase. Though none are specific, certain drugs have been found empirically to be more useful than others in different manifestations of epilepsy. All have certain disadvantages or even dangers. All take a period of time in producing full clinical effect quite unrelated to rates of absorption and excretion. It is unwise, therefore, to judge the efficacy of a drug or dosage until the patient has been under its influence for a considerable period of time—usually a matter of weeks. Changes in type of drug or dosage must be made gradually. Secondly, the sudden withdrawal of one drug which is not achieving a completely satisfactory result, with or without the substitution of another, may initiate a striking recurrence of seizures—even precipitate a dangerous status epilepticus. These drugs must be tapered off as well as on. A third point of value lies in the timing of dosage. The administration of phenobarbital, for instance, to a patient with purely nocturnal attacks is more effectively made in the evening, with morning of course being a better choice for one with purely diurnal seizures. Similarly, increases in dosage may be made prior to menstrual periods if such have been known to be accompanied by increased seizure incidence.

Four drugs are now in common use in the treatment of epilepsy: the bromides, phenobarbital, dilantin, and tridione. Since they have been considered in detail by Dr. Butler, I propose merely to touch on certain clinical aspects of their use.

The bromides are now little used as a basic medication despite the tremendous advance made by their introduction some ninety years ago. Their effects are capricious and depend on associated chloride levels. They are cumulative and, with prolonged heavy dosage, can readily lead to evidence of toxicity—skin

lesions, mental dulling, emotional and psychotic changes. Nevertheless, the addition of bromides to other forms of treatment in cases which do not respond completely otherwise may be very effective. For such purposes in an adult, 0.6 gram doses, two, three, or four times a day are useful.

The introduction of phenobarbital added a much more powerful anticonvulsive drug. Its action is relatively rapid, and it can be given parenterally as well in the emergency treatment of status epilepticus. It is the most important routine antiepileptic drug, either by itself or in combination with dilantin. It is most effective in controlling the types of seizures associated with active motor or sensory manifestations—grand mal seizures, Jacksonian attacks, or focal epilepsy. Dosage of from 60 to 180 mg. daily (for an adult) is in most cases adequate, though sometimes it may be necessary to exceed this. Phenobarbital has limitations however. While it is well worth trying in petit mal attacks or akinetic seizures, the results are unpredictable. Some patients respond well, others do not. There is increasing evidence that its use in psychomotor episodes may even increase their frequency and this possibility must be borne in mind. Toxic effects are unusual with common therapeutic doses, though less rare with children. Larger doses may produce drowsiness, and this constitutes its greatest disadvantage. This can be counteracted, but only to some extent, with benzedrine or caffeine. Less common are mild ataxia or emotional changes. Rashes may rarely appear.

Dilantin, like phenobarbital, has its greatest effect on grand mal, Jacksonian, and focal seizures. Furthermore, evidence is accruing of a definite effect in the reduction of psychomotor attacks. It has the distinct advantage of being unassociated with mental clouding or drowsiness. It is generally used therefore as a basic medication in doses (for an adult) of 0.3–0.4 grams or more daily. It too, has certain limitations. The achievement of a dilantin effect is slower than that with phenobarbital. Some cases will respond more effectively to it than to phenobarbital—others, less well. Not infrequently its administration produces some degree of gastric distress so that its ingestion with meals is desirable. It is often indeed difficult to give it at other times. For these various reasons, its use is commonly augmented by smaller morning and/or evening doses of phenobarbital. Dilantin has, apart from the absence of drowsiness, more frequent toxic effects than phenobarbital. Skin eruptions sometimes occur. Enlargement of the gums may be distressing. Less commonly in adults, but not too infrequently in children, ataxia, diplopia, nystagmus, may appear.

The handling of patients suffering from seizures which are characterized essentially by lack or restriction of function, as opposed to those with striking motor and behavior changes, has always been difficult. I refer to petit mal and akinetic seizures. In both of these, the use of the above-mentioned drugs is often disappointing. Fortunately, the natural course of both is often a fluctuant one, and frequently one tending towards spontaneous improvement. This is especially true in children. However, this is far from the common experience. There is a real need for a drug with a specific effect on these forms. Tridione, which was

originally given clinical trial as an anticonvulsant material, has certainly met with some success in the treatment of both petit mal and akinetic attacks. The time has not yet come to assess its value adequately. In a recent report on 175 patients who had previously resisted all attempts at control, Lennox reported one-third as free of seizures, one-third as having less than one-quarter the previous number of attacks, one-third as unchanged. He used doses of 0.3 grams two, three, or four times daily. Other reports are somewhat less enthusiastic. Most clinicians who have used tridione have had the distressing experience, at one time or another, of finding major seizures appear for the first time in a patient with petit mal.

The toxic effects of tridione are likewise not yet clearly realized nor perhaps recognized. All patients under such therapy witness hemeralopia—an increased visual sensitivity to light—which may, or may not, be very distressing. Skin eruptions occur. Apparently the most dangerous effect is on the blood leucocytes. There is a tendency to neutropenia, and a check on this must be made frequently. At least three cases of fatal agranulocytosis have been reported so far. It seems, therefore, that in this drug we have a material which is more effective than other measures in the treatment of petit mal and akinetic seizures. It has, however, undesirable effects and dangerous possibilities. I think a wise plan at present is to reserve its use until the effects of all other measures, and of time, have been well assessed.

Dr. Harvey: Since Dr. Walker has been interested in the problem of focal epilepsy I will ask him to open the discussion.

Dr. A. Earl Walker: I have been particularly interested in focal epilepsy, i.e., convulsive seizures that develop due to a lesion in the cerebral cortex. The first question raised is "why do some people develop convulsive seizures when they have a brain lesion and others do not?" It has been suggested that a constitutional factor is responsible, a factor related to the cerebral dysrhythmia found in 15% of normal individuals However, there is no clinical evidence for such a view. Ziskind studied patients with focal epilepsy and found no higher familial incidence of epilepsy among the relatives of such patients than in the normal population. Penfield and Erickson came to a similar conclusion. In the last war, in a series of 250 cases of post-traumatic epilepsy which we studied, the incidence of epilepsy in the families of the patients was no higher than in the general population.

We have been interested in the course of focal epilepsy. The attacks seemed to indicate that one part of the brain is responsible and that the attacks spread from that area. But the electro-encephalogram often indicates a generalized dysrhythmia. Is this the end result of a focal lesion or did the patient have a cerebral dysrhythmia originally? In practical terms, suppose a child of two or three years of age has a head injury and develops focal fits and at the age of ten years the electro-encephalogram looks like a generalized dysrhythmia, would removal of the original focus at the age of two or three have prevented the development of a generalized dysrhythmia?

To that question we have no definite answer, but there is some experimental evidence on this point. We have placed wax pellets of penicillin on the brain surface of monkeys, inducing a Jacksonian attack. After a short time the electro-encephalogram, instead of showing a focal abnormality, shows a generalized dysrhythmia; in other words electro-encephalographic alterations occur not only at the site of the pellet but also on the opposite side of the brain. The experimental epileptogenous focus may affect the entire brain so that it gives rise to a generalized dysrhythmia.

We encountered another problem in studying focal epilepsy. In many instances we did not see the attack and had only the patient's vague description of it. To determine the characteristics of the attack, focal or generalized, we attempted to activate the potential epileptogenous foci. Many techniques and drugs were tried but metrazol in small doses was found to reproduce best the clinical seizure. Moreover, 2 cc. of metrazol will cause electro-encephalographic attacks without inducing the clinical fit, so that the locus of the firing zone may be determined in relation to a cranial defect or scalp wound.

In the case of brain wounds, the focus lies about but never in the actual scar. One cannot elicit an attack by stimulation of the scar, but, if the appropriate part of the margin of the scar is stimulated, the attack occurs and is precisely the same as that which the individual has spontaneously. The focus determined by metrazol activation appears to be constant. It is in the same place today and tomorrow. Occasionally we found multiple epileptogenic foci.

Dr. Theodore Lidz: Can one safely assume if a dose of 2 cc. of metrazol is given that a normal individual will not have an attack, whereas an epileptic will?

Dr. Walker: The answer to that question is probably yes, although we do not have a large series of normal individuals. In posttraumatic epileptics, 2 cc. of a 10% solution of metrazol on a primary single test will give rise to convulsive manifestations in 45 per cent of cases. By repeating the test you can bring the percentage up to 67 per cent. There are 30 per cent of posttraumatic epileptics who will not have a seizure by this technique. In the idiopathic seizures the incidence is a little bit higher. Dr. Jasper has given the metrazol somewhat more slowly and can precipitate electro-encephalographic attacks in 85% of the cases of idiopathic epilepsy. Approximately 10% to 15% of the patients will have clinical generalized attacks, another 5% focal manifestations, the other 80% will have no clinical evidence of a fit. The chances are one in seven of producing a clinical seizure, whereas the chances of electro-encephalographic manifestations are eight in ten.

Dr. Leonard J. Gallant: There are some points I would like to bring up about the effect of drugs on the electro-encephalogram. First of all, with the average anticonvulsive doses of the medications mentioned there is no effect on the brain wave in normal people. In epileptics—I'd like to confine my remarks to the idiopathic kind—either they show no effects, or in most cases more abnormalities ap-

pear. Many larval attacks not shown spontaneously become more easily seen. With tridione, for example, we see an increase in the high voltage activity in the electro-encephalogram. Tridione will enhance the faster attacks which are like grand mal attacks. Any hypnotic given to the point of anesthesia enhances the abnormal components of the electro-encephalogram. Dilantin increases the slower component of the brain wave, and many of these people who are treated for grand mal, after treatment begin to show petit mal. Finally, since diagnosis is the first step in treatment I have felt epilepsy should be a clinical diagnosis, and the brain wave should be used as an adjunct because fifteen per cent of epileptics may not show any abnormality in the test and fifteen per cent of non-epileptics may show abnormalities.

Question: How often does hyperventilation precipitate grand mal in an epileptic subject?

Dr. Gallant: In one study the investigators kept the patients hyperventilating until a fit occurred. They found 37 per cent had seizures. Hyperventilation for three or four minutes will not generally precipitate convulsions in the epileptics. Hyperventilation for five to seven minutes will bring about convulsive episodes in a considerable number of patients.

Dr. Harvey: Would Dr. Woolsey care to make a few comments?

Dr. Clinton N. Woolsey: The subject as you have been considering it today has been clinical in its point of view. However, some recent results from the physiological laboratory may be pertinent and of ultimate practical interest for the surgical treatment and the diagnosis of epilepsy.

I suppose it is generally held that epileptic discharges from the cerebral cortex make use chiefly of the pyramidal tract and that this tract originates in the precentral motor cortex. There is increasing evidence that only a portion of the pyramidal tract originates in the so-called "motor cortex." We have recently applied a new technique to the study of this problem, and have undertaken to map the cortical origins of fibers traversing the medullary pyramid by stimulating the pyramid electrically and recording the potential changes produced in the cortex by the arrival of impulses conducted antidromically in the pyramidal axones. By this method it has been possible to confirm and extend the evidence regarding the regions of cortex contributing fibers to the pyramidal tract. The regions include areas four and six precentrally and the entire parietal lobe in the monkey and homologous areas in cat and rabbit.

The largest contribution apparently does indeed originate precentrally but there is also a very considerable part of the pathway which comes from the postcentral gyrus. Moreover, there is special interest in the pyramidal fibers whose cells are in that portion of the parietal cortex which forms the upper bank of the

sylvian fissure in the monkey and the homologous region in other species. This is the locus of a second somatic afferent area, so the region both receives and discharges. In the experimental animal discharges from this area can give rise to epileptiform convulsions of the Jacksonian type. Rasmussen and Penfield recently have reported data suggesting the existence of a similar system in man. Thus it should be important for diagnosis and surgical therapy to keep in mind the existence of efferent pathways not originating in the precentral motor cortex, especially since failure to consider this parietal motor system could lead to mistaken localization of an epileptogenic focus.

Dr. Harvey: There is still a great deal to be learned about epilepsy, nevertheless we are faced with the management of a large number of cases with a still inadequate armament. Emotional problems are important and I wonder if Dr. Lidz would care to comment.

Dr. Theodore Lidz: The psychiatric management of patients with epilepsy has been admirably discussed by Dr. Magladery. I should like to mention only one other point. When a patient has been rendered free of seizures by proper management and is apparently in a state of equilibrium, it sometimes happens that symptoms suddenly reappear. This recrudescence may be brought about by some minor emotional irritation on the part of the patient, and often superficial psychotherapy will effect a subsidence of symptoms. I would urge you to try such simple measures before undertaking extensive changes in drug regimens.

Dr. Gallant: Dr. Lidz' remarks lead to another interesting matter. Some epileptics may use their attacks for ego satisfaction. By preventing these attacks, the patient is robbed of this outlet and may develop other symptoms.

SUMMARY

The rational management of epilepsy depends on the separation of symptomatic seizures caused by brain tumors, syphilis, etc., from the "cryptogenic" variety. Only when specific causes can be excluded is it safe to proceed solely with measures to suppress the seizures. Such suppression is effected largely by drugs and by control of emotional factors. Secondary but important considerations are the avoidance of alcohol and of other situations wherein an attack would endanger the patient or others. Dehydration and ketogenic diets have infrequent usefulness in the modern therapy of epilepsy.

Emotional and social rehabilitation is one of the key points in the proper management of epileptics. Such factors play an important role in the precipitation and in the frequency of attacks. More serious is the impact of repeated attacks on the psychological development and adjustment of the individual to school, work, and social situations.

The drugs of greatest usefulness are phenobarbital and dilantin. Bromides are not much used because of toxicity. Tridione has been successful in the suppression of petit mal and akinetic seizures, but it occasionally causes agranulocytosis and has other unpleasant side effects. Methods of animal screening have been improved and it is to be hoped that more potent and less toxic agents will be forthcoming. Animal experimentation has demonstrated also that a focal lesion of the cortex may give rise later to a generalized dysrhythmia, and secondly that cortical areas other than those of the motor cortex participate in motor phenomena.

PHYSIOLOGICAL STUDIES IN CONGENITAL HEART DISEASE[1]

V. The Circulation in Patients with Isolated Septal Defects

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In three of the preceding papers of this series various types of congenital heart disease have been discussed (1, 2, 3). This report presents the physiological studies made in a group of individuals with isolated septal defects. Five cases with these lesions were selected as being most representative of the various clinical aspects of this anomaly. These cases will be presented in a sequence of increasing clinical disability to clarify the relationship between the degree of incapacity and the physiological data obtained.

METHODS

The methods used in these studies have been described in detail and evaluated in the first paper of this series (4). The Fick principle has been applied to determine the blood flow through various parts of the circulation. A restatement of the formulae based upon this principle and a definition of terms is made at this point for clarity.

a. Systemic flow is the volume of blood passing through the peripheral vessels per minute.

$$\text{Systemic Blood Flow (ml. per minute)} = \frac{O_2 \text{ uptake (ml. per minute)} \times 100}{O_2 \text{ content of peripheral arterial blood (volume per cent)} - O_2 \text{ content right auricular blood (volume per cent)}}$$

b. Pulmonary artery flow is the volume of blood passing through the pulmonic valve into the pulmonary artery per minute.

$$\text{Pulmonary Artery Flow (ml. per minute)} = \frac{O_2 \text{ uptake (ml. per minute)} \times 100}{O_2 \text{ content of pulmonary vein blood (volume per cent)} - O_2 \text{ content pulmonary arterial blood (volume per cent)}}$$

[1] Supported by grants from the Commonwealth Fund and the Carolyn Rose Strauss Foundation.

If the oxygen content of pulmonary vein blood is not measured directly, it is assumed to be 95 per cent of the oxygen capacity. If blood of the pulmonary artery is not obtained, a sample taken from the right ventricle near the pulmonic valve (the outflow tract) is substituted.

c. From a and b it may be computed that

$$\text{Shunt (ml. per minute) right to left} = \text{Systemic flow} - \text{Pulmonary artery flow}$$

or

$$\text{Shunt (ml. per minute)} = \text{left to right} = \text{Pulmonary artery flow} - \text{Systemic flow}$$

The formulae permit an estimation of the volume and overall direction of the intracardiac shunt. Nevertheless, an analysis of the oxygen contents gives evidence that reciprocal admixture does occur.

d. Effective pulmonary flow is that volume of mixed venous blood which, after its return to the right auricle, ultimately reaches the pulmonary capillaries.

$$\text{Effective pulmonary flow (ml. per minute)} = \frac{\text{O}_2 \text{ uptake (ml. per minute)} \times 100}{\text{O}_2 \text{ content of pulmonary vein blood (volume per cent)} - \text{O}_2 \text{ content right auricular blood (volume per cent)}}$$

Bloods for analysis from the various parts of the circulatory system were obtained by cardiac catheterization, following the method of Cournand (5), and by direct arterial puncture. Blood gas analyses were carried out in the manometric apparatus of Van Slyke and Neill (6). Arterial and intracardiac pressures were optically recorded by means of a Hamilton manometer (7), and mean pressures were calculated by planimetric integration of the area under the curve. Respiratory gases were collected in Douglas bags and analyzed in the Haldane apparatus (8) and corrected to standard temperature and pressure. Resistance in the pulmonary circuit was calculated by Aperia's formula (9). The standard exercise test referred to is described in an earlier communication (4), and its interpretation and significance therein discussed.

The shortcomings inherent in the application of the above formulae have been discussed in connection with the determination of pulmonary artery flow in the presence of a ventricular defect (4). Similarly, the calculation of systemic flow is complicated by reciprocal admixture through an auricular septal defect. This necessitates the use of the oxygen content of blood from the superior vena cava as representative

of mixed venous blood. This may provide an error in the results, since it has been shown that true mixture of venous blood does not occur before the outflow tract of the right ventricle (5).

All the cases presented in this report fulfill the physiological criteria for the presence of septal defects, although in none has the diagnosis been confirmed by postmortem examination (10, 11). An auricular septal defect is present when the oxygen content of the right auricular blood exceeds that of blood from superior vena cava blood by about 2 volume per cent. A similar difference between right auricular and right ventricular blood demonstrates the presence of a ventricular septal defect. Direct evidence of such defects may be obtained when the left chambers of the heart are catheterized.

Case 1. A. G. A. (age 10, date of study November 12, 1947). The birth and development of this child were normal. When the patient was 2 months old the family physician diagnosed heart disease. At the age of two years he had an episode of slight cyanosis and momentary loss of consciousness. Two similar episodes followed within six months, but there were no further recurrences. At the time of examination he suffered no incapacity.

On physical examination there was no clubbing or cyanosis. The positive findings were limited to the heart. The blood pressure in the arm was 105/70. There was a marked thrill over the precordium, maximal in the left second interspace. There was a very loud, widely transmitted systolic murmur over the precordium, maximal in the second and third interspace, and a long, blowing, much fainter diastolic murmur along the left sternal border.

On fluoroscopy, the heart was of normal size, with a prominent pulmonary conus. Pulmonary pulsations of normal degree were seen. By x-ray, some right auricular enlargement was seen in the LAO position. The ECG was normal. Routine laboratory studies revealed a hematocrit of 38, hemoglobin of 12.0 grams, and a red count of 4.6 million.

Physiological studies: The standard exercise test was not performed. Pertinent data obtained during cardiac catheterization are shown in Table I. Significant findings are as follows:

1. The oxygen content of right ventricular blood exceeded that of right auricular blood by 4.6 volume per cent. The oxygen content of pulmonary arterial blood was 3.4 volume per cent higher than that of right auricular blood.
2. The oxygen saturation of peripheral arterial blood was 99 per cent.
3. The pulmonary arterial pressure was 30/10, with a mean pressure of 20 mm. Hg.

Comment: The rise in oxygen content from right auricular to right ventricular blood indicates the presence of a ventricular septal defect allowing admixture of oxygenated blood with the venous blood. The

slightly lower oxygen content of the pulmonary arterial blood may be due to the fact that the right ventricular sample was taken as the catheter tip lay near the septal defect. The overall shunt is 5260 cc./min./M_2 directed from left to right as shown by the fact that the pulmonary artery flow exceeds the systemic flow.

The full saturation of the peripheral arterial blood, as well as the equality of systemic and effective pulmonary flow, indicate that the shunt is directed entirely from left to right with no reciprocal admixture (Fig. 1).

TABLE 1

Date obtained from right heart catheterization

CASE NUMBER	DATE	NAME	SEX	AGE	SURFACE AREA (M_2)	O_2 CONSUMPTION (cc.)	CO_2 PRODUCTION (cc.)	RQ	MINUTE VOLUME (L/M)	BMR	SVC O_2 (VOL. %)	RA O_2 (VOL. %)	RV O_2 (VOL. %)	PA O_2 (VOL. %)	PV O_2 (VOL. %)	ARTERIAL BLOOD		CARDIAC OUTPUT		SHUNT (L/M/M2)	EFFECTIVE (L/M/M2)
																Capacity (vol. %)	Saturation (%)	Pulmonary (L/M/M2)	Systemic (L/M/M2)		
1	11/12	AGA	M	10	0.93	128	103	0.79	3 7	−18	13.8	12.6	17.2	16.0	17.8	17.9	99.0	7.96	2.70	5.26 L-R	2.7
2	9/30	AW	M	9	1.16	154	67	0.37	5.2	−23	13.6	13.9	16.3	15.4	18.8	19.8	91.0	3.91	3.24	0.67 L-R	2.7
3	10/28	VE	F	27	1.18	122	100	0.81	5.0	−18	12.0	15.7 14.5	17.7	15.0 15.7	19.5	20.5	90.0	2.50	1.65	0.86 L-R	1.4
4	9/16	GD	M	16	1.72	252	248	1.0	11.4	+8	15.9	17.9		18.7	24.3	25.6	79.5	2.62	3.33	0.71 R-L	1 7
5	4/2	LG	M	30	2.0	145	167	1.16	6.8	−21	19.1	20.8	20.8	20.7	32.0	33.6	70.5	1.23	4.78	3.55 R-L	1.2

Case 2. A. J. W. (age 9, date of study September 30, 1947). This child was apparently normal at birth. Except for a single attack of unconsciousness with convulsions at the age of three months, his development was unremarkable. When he was five days old the family physician noted that he had a cardiac murmur. For six months prior to admission he had occasional precordial pain, unrelated to exercise. Slight dyspnea began at this time and subsequently increased, although it remained moderate and caused the patient no apparent incapacity.

On physical examination there was no clubbing or cyanosis. The positive findings were limited to the heart. The blood pressure in the arm was 102/48. The cardiac outline was normal to percussion. There was a systolic thrill distributed over the entire anterior chest wall. In the left first, second and third interspaces a continuous murmur could be heard, but the diastolic component

was much less pronounced than the systolic. On fluoroscopy the heart was of normal size with a prominent pulmonary conus. The vascular markings in the lung fields were increased, but pulsations were normal. On x-ray, both the right auricle and ventricle were seen to be enlarged. The ECG showed left axis deviation and normal left ventricular preponderance. Routine laboratory studies revealed a hematocrit of 38.5, a hemoglobin of 11.9 grams, and a red count of 4.5 million.

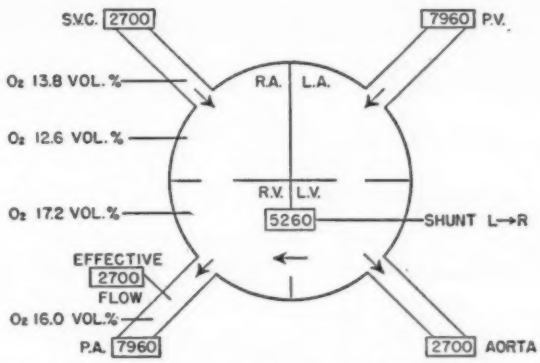

FIG. 1. ILLUSTRATING THE FINDINGS IN CASE 1 (A. G. A.)

The oxygen content of right ventricular blood is significantly higher than that of the right auricular blood, indicating a ventricular septal defect. The pulmonary artery flow exceeds the systemic flow, giving the intracardiac shunt an overall direction of left to right. Since the effective pulmonary flow equals the systemic flow, there is no reciprocal right to left admixture.

Physiological studies: The standard exercise test was not performed. Pertinent data obtained during cardiac catheterization are shown in Table I. Significant findings are as follows:

1. The oxygen content of the right ventricular blood was 2.4 volume per cent higher than that of the right auricular blood.
2. The saturation of the peripheral arterial blood was 91 per cent.
3. The pulmonary artery flow was greater than the systemic flow.
4. The pulmonary arterial pressure was 40/29 with a mean pressure of 34 mm. Hg.

Comment: The rise in oxygen content from right auricular to right ventricular blood indicates the presence of a ventricular septal defect, allowing admixture of oxygenated with venous blood. The overall shunt is 670 cc./min./M_2 directed from left to right, as shown by the

fact that the pulmonary artery flow exceeds the systemic flow. However, reciprocal right to left admixture is demonstrated by the lowered saturation of peripheral arterial blood and by the fact that the effective pulmonary flow was less than the pulmonary artery flow (Fig. 2).

Case 3. V. E. (age 27, date of study October 20, 1947). This patient was a Lorain type dwarf. Her birth was not remarkable. Her developmental history was normal except for lack of growth. For as long as she could remember she had known she had heart disease. Although she had had some exertional dyspnea

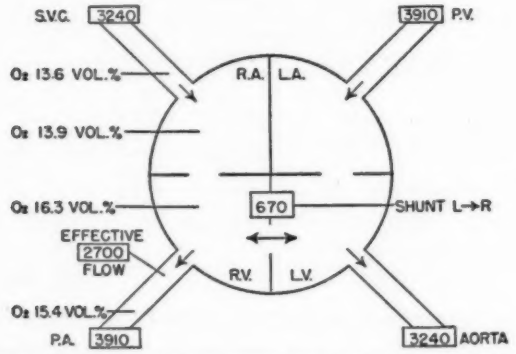

FIG. 2. SHOWING THE FINDINGS IN CASE 2 (A. J. W.)

The oxygen content of right ventricular blood is significantly higher than that of the right auricular blood, indicating a ventricular septal defect. The pulmonary artery flow exceeds the systemic flow, giving the intracardiac shunt an overall direction of left to right. Since the effective flow is lower than the systemic flow, there is reciprocal admixture from right to left.

while in school, it had not been progressive, nor had she ever manifested cyanosis. In 1933 she became pregnant and, suffering some increase in her dyspnea, was hospitalized. The child was delivered by Caesarean section. An ECG in March of that year showed left axis deviation and myocardial damage. The patient was not seen again until January 1947, at which time she was having increasing exertional and nocturnal dyspnea. Her liver and spleen were enlarged. She was digitalized, but continued to suffer intermittent bouts of decompensation.

On physical examination at the time of the present study, the positive findings were limited to the heart, except for the traits of dwarfism. There was no clubbing or cyanosis. The blood pressure in the arm was 110/70. The heart was enlarged to the left. There was a loud systolic murmur and thrill in the left second interspace, transmitted all over the chest. At the apex there was a harsh, high pitched

systolic blow. There were no diastolic murmurs. X-ray, on September 11, 1947, revealed the heart to be enlarged to the left. The pulmonary artery was prominent and the aorta hypoplastic. Slight enlargement of the right auricle and right ventricle was noted. The ECG showed left axis deviation and bundle branch block. Laboratory studies revealed a hematocrit of 45.5, a hemoglobin of 13.8 grams, and a red count of 4.9 million. Circulation time (decholin) was 10 seconds.

Physiological studies: The standard exercise test showed a rise in oxygen consumed per liters of ventilation (Table II). Pertinent data obtained during cardiac catheterization are shown in Table I. Significant findings are as follows:

1. The oxygen content of the right auricular blood was 2.5 volume per cent higher than that of the blood of the superior vena cava. The oxygen content of the right ventricular blood was 2.0 volume per cent higher than that of the right auricular blood.

TABLE II

Results Obtained from the Standard Exercise Test

CASE NO.	DATE	NAME	SEX	AGE	OXYGEN CONSUMED PER LITER VENTILATION (CC.)		CO_2 PRODUCED PER LITER VENTILATION (CC.)
3	9/11/47	VE	F	27	Rest	21.5	17.8
					Exercise	24.3	19.7
4	7/17/47	GD	M	23	Rest	16.1	19.6
					Exercise	17.5	18.0
5	3/11/47	LG	M	30	Rest	21.3	24.5
					Exercise	46.0	23.7

2. The oxygen saturation of the peripheral arterial blood was 90 per cent.
3. The pulmonary arterial blood flow exceeded the systemic flow.
4. The pulmonary arterial pressure was 49/20 with a mean pressure of 39 mm. Hg.

Comment: The rise in oxygen content of blood from superior vena cava to right auricle indicates the presence of an auricular septal defect allowing left to right admixture of blood. A further rise in oxygen content of the blood from right auricle to right ventricle indicates the presence of a ventricular septal defect. The overall shunt is 855 cc./min./M_2 directed from left to right as shown by the fact that the pulmonary artery flow exceeds the systemic flow and that the effective pulmonary flow is lower than pulmonary artery flow. Re-

ciprocal right to left admixture through the defects is indicated by the lowered saturation of peripheral arterial blood.

In the calculation of the systemic flow, the oxygen content of blood from the superior vena cava was used. This resulted in an overall shunt directed to the right. If higher oxygen content of blood were substituted in the Fick equation, the calculated systemic flow would exceed the pulmonary artery flow. From this calculation the overall

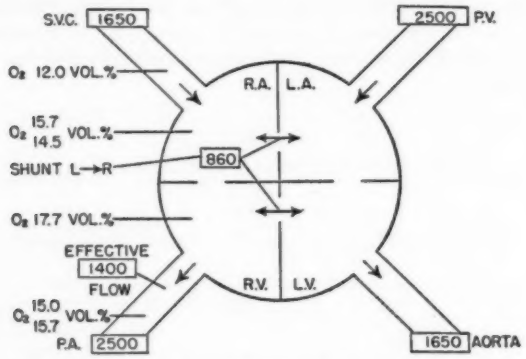

FIG. 3. SHOWING THE FINDINGS IN CASE 3 (V. E.)

The oxygen content of the right auricular blood is significantly higher than that of the superior vena cava. The oxygen content of the right ventricular blood is significantly higher than that of the blood of the right auricle. Auricular and ventricular septal defects are thereby indicated. The pulmonary artery flow exceeds the systemic flow, giving the intracardiac shunt an overall direction of left to right. Since the effective flow is lower than the systemic flow, there is reciprocal admixture from right to left.

shunt would be directed toward the left. It is evident, therefore, that calculation of shunts in patients with septal defects, except for their order of magnitude, are at best approximations (Fig. 3).

Case 4. G. D. (age 16, date of study September 16, 1947). The patient's birth and development were normal. When he was two years old his parents were informed by a physician that he had a "cardiac condition." When he was ten his parents first noted marked dyspnea and mild cyanosis on moderate exertion. Despite a progression of these symptoms, he had no convulsions, paralysis or loss of consciousness. Although he could walk half a mile, climbing stairs caused extreme dyspnea.

On physical examination the patient was seen to be mildly cyanotic with slight clubbing of the fingers. The blood pressure in the arm was 104/78. The thorax was asymmetrical, bulging slightly on the left side. The heart was within normal limits of size to percussion. There was a rough, moderately loud systolic murmur heard best at the left sternal border in the fourth interspace and transmitted to the apex. The second pulmonic sound was snapping and was louder than the second aortic sound. On fluoroscopy the size of the heart was normal. The pulmonary conus was prominent and the pulmonary artery was large and quiet. The ECG showed right axis deviation and right ventricular hypertrophy with a slight delay in interventricular conduction time. Laboratory studies revealed a hematocrit of 43.5, a hemoglobin of 14 grams, and a red count of 5.3 million.

Physiological studies: The standard exercise test showed a rise in the oxygen consumed per liters of ventilation (Table II). Pertinent data obtained during cardiac catheterization are shown in Table I. Significant findings are as follows:

1. The oxygen content of the right auricular blood was 2.0 volume per cent higher than that of the blood of the superior vena cava.
2. The oxygen saturation of the peripheral arterial blood was 79.5 per cent.
3. The systemic blood flow exceeded the pulmonary artery flow.
4. The pulmonary arterial pressure was 74/47 with a mean pressure of 64 mm. Hg.

Comment: The rise in oxygen content of blood from the superior vena cava to right auricle indicates the presence of an auricular septal defect. The overall shunt is 710 cc./min./M_2 directed from right to left as shown by the fact that the systemic flow exceeds the pulmonary artery flow. The low saturation of the peripheral arterial blood and the fact that the effective pulmonary flow is lower than the pulmonary artery flow give further evidence of the right to left shunt. However, the rise in oxygen content from superior vena cava to right auricular blood shows reciprocal admixture from left to right through the auricular septal defect (Fig. 4).

Case 5. L. G. (age 30, date of study April 2, 1947). The patient recalls only that his mother restricted his activity and that he had two episodes of epistaxis during his childhood. He was supposed to have been cyanotic at birth and during childhood, and to have suffered easy fatigue and dyspnea. As far back as he can recall, he has had some degree of cyanosis of the nailbeds and lips aggravated by exertion and cold. He became dyspneic on mild exercise.

On physical examination, slight clubbing and cyanosis were noted. The remaining positive findings were limited to the heart. The blood pressure in the left arm was 90/76; in the right arm, 112/92. The heart was normal in size to percussion. There was no thrill. There was a short blowing systolic murmur

at the lower left sternal border. In the fifth interspace at the sternal edge a short high-pitched systolic murmur was well localized. Neither murmur was transmitted. On fluoroscopy the size of the heart was normal. There were increased vascular markings with minimal pulsations in the lung fields. The pulmonary arteries were large. The ECG showed right axis deviation, right ventricular hypertrophy, and right bundle branch block. Laboratory studies revealed a hematocrit of 71.2, a hemoglobin of 21.8 grams, and a red count of 9.8 million. Angiocardiography gave equivocal results.

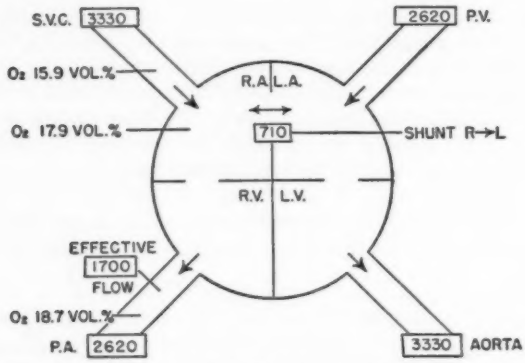

FIG. 4. ILLUSTRATING THE FINDINGS IN CASE 4 (G. D.)

The oxygen content of the right auricular blood is significantly higher than that of the superior vena cava blood. This indicates the presence of an auricular septal defect. The systemic flow exceeds the pulmonary artery flow, giving the intracardiac shunt an overall direction of right to left. Since the effective flow is lower than the pulmonary artery flow, there is reciprocal admixture from left to right.

Physiological studies: The standard exercise test showed a rise in the oxygen consumed per liters of ventilation (Table II). Pertinent data obtained during cardiac catheterization are shown in Table I. Significant findings are as follows:

1. The oxygen content of the right auricular blood was 1.7 volume per cent higher than the blood from the superior vena cava.
2. The oxygen saturation of the peripheral arterial blood was 70.5 per cent.
3. The systemic blood flow exceeded the pulmonary artery flow.
4. The pulmonary arterial pressure was 103/70 with a mean pressure of 82 mm. Hg.

Comment: The rise in oxygen content of blood from superior vena cava to right auricle indicates the presence of an auricular septal defect

through which left to right admixture is occurring. However, the overall shunt of 3550 cc./min./M_2 is directed from right to left as shown by the fact that the systemic flow exceeds the pulmonary artery flow. Further manifestations of this right to left shunting are found in the reduced peripheral arterial saturation, and in the fact that the effective pulmonary flow is lower than the pulmonary artery flow (Fig. 5).

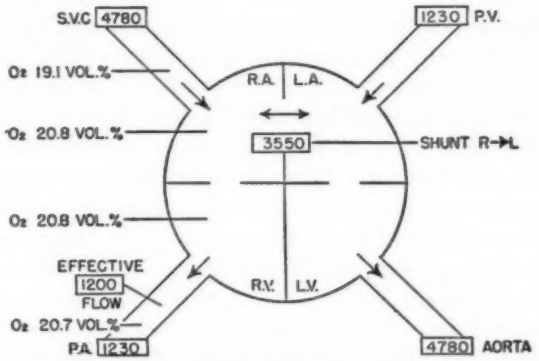

FIG. 5. SHOWING THE FINDINGS IN CASE 5 (L. G.)

The oxygen content of the right auricular blood is significantly higher than that of the superior vena cava blood. This indicates the presence of an auricular septal defect. The systemic flow exceeds the pulmonary artery flow, giving the intracardiac shunt an overall direction of right to left. Since the effective flow is lower than the pulmonary artery flow, there is reciprocal admixture from left to right.

DISCUSSION

A review of the histories of the five patients presented in this report reveals that all had cardiac disease since childhood. Their commonest presenting complaints were exertional dyspnea and intolerance to exercise.

Physical examination showed certain pertinent facts. Two of the patients exhibited cyanosis and digital clubbing. In only one instance (Case 3, V. E.) was the heart enlarged to percussion. All five patients had systolic murmurs of varying degrees, intensities, distribution, and transmission. Two patients (Case 1, A. G. A.; Case 2, A. J. W.)

had diastolic murmurs at the second and third interspace at the left sternal border. On fluoroscopy, only one patient (Case 3, V. E.) had cardiac enlargement, but a prominent pulmonary conus was revealed in three patients (Case 1, A. G. A.; Case 2, A. J. W.; Case 4, G. D.). The ECG was normal in the first patient, showed right axis deviation in the patients with auricular septal defects (Case 4, G. D.; Case 5, L. G.) and left axis deviation in those with ventricular septal defects (Case 2, A. J. W.; Case 3, V. E.). Laboratory data revealed normal hematocrits, hemoglobins, and red counts in all but one patient (Case 5, L. G.) who had a marked polycythemia.

As part of the physiological studies conducted in this group, three of the patients performed the standard exercise test. In all there was a rise in the oxygen consumed per liter of ventilation (Table II). This finding is in contrast with the results obtained in the study of patients with tetralogy of Fallot (1). In these latter there was generally a fall in the ratio of oxygen consumed per liter of ventilation during exercise. Conversely, in the present group under study, as in normal individuals and in patients with the Eisenmenger complex (2) the rise in oxygen consumed per liter of ventilation during exercise demonstrates that the effective pulmonic blood flow can increase significantly with exercise.

The other physiological studies showed changes paralleling the variations in clinical findings. A comparison of the blood flows revealed that three patients (Case 1, A. G. A.; Case 2, A. J. W.; Case 3, V. E.) had shunts which were predominantly from left to right. Two patients showed overall right to left shunts (Case 4, G. D.; Case 5, L. G.). In these two latter patients cyanosis was marked and the saturation of the peripheral arterial blood was low (Table I).

Pulmonary factors concerned with oxygen transfer in the lung are apparently not involved in this decrease in the saturation of peripheral arterial blood. In 16 cases in which it was possible to catheterize the pulmonary vein, the blood returning to the heart from the lungs was fully saturated. Therefore, arterial unsaturation is probably due to the reduction in the percentage of mixed venous blood perfusing the lung, which results from intracardiac shunting from right to left (12).

The intracardiac shunting of blood is expected to be predominantly directed to the right in the presence of a normal total cross sectional

area of the pulmonary arterial bed and in the absence of pulmonic stenosis. The finding in two of these cases that the shunt is predominantly directed to the left, implies an increase in the resistance of the pulmonary vascular tree. In this respect these cases show a disturbance of their pulmonary hemodynamics comparable to that seen in Eisenmenger's complex (2).

Two other observations support the finding of increased pulmonary resistance. First, the blood pressure in the pulmonary artery is increased in both systolic and diastolic components (Table III). Second, calculation of the loss of pressure head in the pulmonary

TABLE III

Intracardiac and Peripheral Blood Pressures. Resistances in Pulmonary and Peripheral Circulation

CASE NO.	DATE	NAME	SEX	AGE	FEMORAL ARTERY			SYSTEMIC FLOW (L/M/M2)	RESISTANCE (DYNES/CM5/SEC.)	RV		PA			PA FLOW (L/M/M2)	RESISTANCE (DYNES/CM5/SEC.)
					Systolic	Diastolic	Mean			Systolic	Diastolic	Systolic	Diastolic	Mean		
1	11/12	AGA	M	10	105	61	76	2.7	2,252	32	8	30	10	20	7.9	197
2	9/30	AW	M	9	155	71	106	3.2	2,650	40	29	40	29	34	3.9	695
3	10/28	VE	F	27	142	87	107	1.7	5,050	72	3	49	20	39	2.5	1,245
4	9/16	GD	M	23	136	88	103	3.3	2,470	74	32	74	47	64	2.6	1,970
5	4/2	LG	M	30	100	73	77	4.8	1,290	103	0	103	70	82	1.2	5,450

circuit reveals that the greatest elevation of resistance occurs in patients with right to left shunts (Table III).[2] In one of these cases (5, L. G.) the resistance approaches the magnitude of that seen in Eisenmenger's complex.

The increase in resistance is further reflected in the work of the right ventricle. The subject of the work of the heart and the assumptions necessary for its computation have been discussed in a previous paper of this series (2). Table IV demonstrates that the relative work of the two ventricles changes as the pulmonary resistance increases. The significant fact which appears from these

[2] Normal resistance = 480 dynes/cm.^{5}/sec. Calculated according to Aperia's formula (9) using a normal mean pulmonary arterial pressure of 18 mm. Hg (13) and normal cardiac index.

calculations concerns the ratio of the velocity energy of the ventricle to its total work.[3] In normal individuals the ratio, velocity energy/total work, for the right ventricle is five times as great as this ratio for the left. Table IV shows that only in Case 1 (A. G. A.) is the ratio within normal range. In Case 2 (A. J. W.) and Case 4 (G. D.) the ratio is 3/1 and 1/1 respectively. It would seem, therefore, that an increasing amount of the energy of the right ventricle is dissipated in overcoming the increased resistance in the pulmonary vascular tree.

Thus, evidence of increased resistance in the pulmonary vascular circuit is furnished by four findings: (1) intracardiac shunting of blood from right to left; (2) the presence of pulmonary arterial hypertension; (3) the marked loss of pressure head in the pulmonary circulation which becomes apparent when resistance is calculated; and (4) the changes in the ratio, velocity energy/total work, of the two ventricles.

The causes of increased pulmonary resistance in cases of septal defect have been discussed by a series of investigators. First, the underlying mechanism for predominant left to right shunting has been elucidated. Uhley proposed in 1942 that gravity alone was the cause for the direction of this shunt. This investigator doubted explanations which were based upon differences in auricular pressures (15). However, recent work by Brannon, Weens, and Warren (10), and by Cournand and his group (16) has demonstrated by direct measurements that the left auricular pressure exceeded the right in cases in which both auricles were catheterized. These studies indicate that flow through the septal defect is ordinarily from left to right because of this pressure gradient.

[3] The formulae used in these calculations are after Starling (14):

(1) Pressure Energy (gram-cm.) = MP × SD × D Hg.
  a. MP = Mean pressure in pulmonary artery or aorta.
  b. SD = Systolic discharge (cc./minute) = Min. vol. (cc. min.)/Pulse rate.
  c. D Hg. = Specific gravity mercury/10.

(2) Velocity Energy (Gram-cm.) = Va × SD/2g.
  a. g = gravity constant (980)
  b. Va = Velocity of blood in pulmonary artery or aorta (cm./sec.)
    i. Va = SD/ Ca × ET
      A. Ca = Cross section ($cm.^2$) pulmonary artery or aorta
      B. ET = Systolic ejection period (sec) = $\frac{60/\text{pulse rate}}{8/3}$

TABLE IV

The Work of the Heart in Three Cases of Septal Defect

CASE NUMBER	DATE	NAME	SEX	AGE	RIGHT HEART									LEFT HEART								Rt. Vel./Rt. Work / Lt. Vel./Lt. Work Ratio
					Systolic Discharge (cc.)	Cross Section Area (cm.²)	Systolic Ejection Time (sec.)	Velocity (cm./sec.)	Velocity Energy (gram-cm.)	Pressure Energy (gram-cm.)	Mean Pressure (mm. Hg)	Total Work (gram-cm.)	Velocity Energy / Total Work × 100	Systolic Discharge (cc.)	Cross Section Area (cm.²)	Systolic Ejection Time (sec.)	Velocity (cm./sec.)	Velocity Energy (gram-cm.)	Pressure Energy (gram-cm.)	Mean Pressure (mm. Hg)	Total Work (gram-cm.)	Velocity Energy / Total Work × 100	
*Norm.					66.5	5.14	0.3	43.0	1.46	1360	15	1361.5	0.1	66.5	3.9	0.3	57	1.94	9050	100	9051.9	0.02	5
1	11/12	GA	M	10	82.4	5.14	0.25	64.0	2.7	2241.3	20	2244	0.1	28	3.9	0.25	27	0.38	2894.1	76	2894.5	0.013	10
2	9/30	AW	M	9	52.2	5.14	0.27	37.6	1.0	2413.7	34	2414.7	0.041	44.2	3.9	0.27	42.1	0.94	6371.9	106	6372.8	0.015	3
4	9/16	GD	M	23	52.9	5.14	0.27	38.3	1.0	4604.4	64	4605.4	0.021	67.4	3.9	0.27	64.2	2.2	9449.4	103	9451.6	0.023	1

* Values for the work of the normal heart were derived using minute vol. = 5000 cc./min.; pulse rate = 75/min.; cross sec. PA = 5.14 cm.²; cross section aorta = 3.9 cm.²; mean PA pressure = 15 mm. Hg; mean pressure aorta = 100 mm. Hg.

A second approach to the problem of increased pulmonary resistance has dealt with the effects of increased blood flow. Levy and Blalock (17) in experimental observations on dogs with artificial patent ducti arteriosi, and Vandam, Bing, and Gray (3) studying patients with patent ducti arteriosi reach similar conclusions. Their findings suggest that the pulmonary vascular bed can normally accommodate a large rise in volume flow with no rise in the pressure of the peripheral pulmonary vessels. It is apparent, therefore, that normally pulmonary resistance is low.

In the light of these observations, the assumption may be ventured that the increase in pulmonary resistance results from changes in the pulmonary vascular tree. Posselt, in 1909, examined the pulmonary vessels in cases of septal defects and noted sclerotic changes in the large arteries (18). Brenner also noted sclerotic changes in the larger pulmonary arteries in routine autopsies. He did not believe that these were sufficient to increase pulmonary resistance (19). More recently, changes affecting the smaller radicles of the pulmonary vascular tree have been described. Taussig, Harvey, and Follis (20), Burrett and White (21), Johannsen and Connor (22), and Bedford, Parkinson, and Papp (23) have reported these changes in cases of septal defects which have been examined postmortem. However, no attempt has been made to correlate this finding with pulmonary hypertension. One might conjecture that widespread sclerotic changes affecting the smaller vessels, possibly in combination with thrombi, could raise pulmonary resistance. It is impossible to state at this time whether or not such changes are a result of increased pulmonary artery flow or develop as a result of other factors.

On the other hand, the rise in pulmonary resistance may result from increased left auricular pressure rather than from changes in the pulmonary vascular tree. The proof of this must await a method for simultaneous measurement of the pressure in both auricles and in the pulmonary artery. It is doubtful that this mechanism is at work in the cases of this series, since pulmonary congestion which would be expected to accompany such a condition is absent.

In addition to these mechanisms, functional factors have been considered in elevating pulmonary resistance (24, 25). Further investigation is necessary to elucidate this problem.

SUMMARY

Five cases of septal defects have been presented.

In the three cases in which the standard exercise test was performed the consumption of oxygen per liter of ventilation rose.

In three patients the overall direction of the intracardiac shunt was from left to right, and in two the shunt was from right to left. The degree of clinical disability paralleled an increase in pulmonary resistance. Increased resistance in the pulmonary bed was evidence by (a) right to left shunt; (b) elevation of systolic and diastolic pressures in the pulmonary artery; (c) marked loss of pressure head in the pulmonary vascular tree; and (d) changes in the ratio, velocity energy/total work, of the two ventricles. Possible mechanisms for the rise in pulmonary resistance were discussed.

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PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in Hurd Hall, March 8, 1948

*The Experimental Pharmacology and Effectiveness of 3–4, Dimethyl-5-sulfanilamido-isoxazole.** Drs. Morton S. Bryer, Emanuel B. Schoenbach, C. Earl Ott and Perrin H. Long (*Department of Preventive Medicine, The Johns Hopkins University School of Medicine*).

3–4, Dimethyl-5-sulfanilamido-isoxazole is a sulfonamide derivative first described by Schnitzer et al (1). Reports of its use in urinary tract infections have appeared (2, 3). This short report deals with the experimental pharmacology and effectiveness of this sulfonamide derivative.

The L. D. 50 of this sulfonamide derivative for Swiss white mice is approximately 3.5 grams per kilogram when given as the sodium salt by the subcutaneous route. When a single dose of 1.25 grams per kilogram suspended in accacia is administered per os to mice, the average total concentration of the drug in the blood of these animals is 8 mgms. % at 1 hour, 3 mgms. % at 2 hours and 2 mgms. % at 4 hours. In man, following an initial dose of 3.0 grams and then 1.0 gram of the drug q. 4 hours for 48 hours, average concentrations of the drug in the blood were as follows: in 4 hours 4.8 mgms. %; in 8 hours 4.2 mgms. %; in 24 hours 3.7 mgms. %; in 32 hours 3.6 mgms. %; and in 48 hours 4.1 mgms. % respectively. In three test subjects, each of whom received an initial dose of 3.0 grams of this compound and then maintenance doses of 1.0 gram every 4 hours for 48 hours, 46, 51, and 55 per cent of the drug was excreted in a period of 96 hours after the first dose. In man little of the drug was found to be acetylated either in the blood or urine during the 96 hour test period. In both mice and men the amount of the drug entering the red blood cells was approximately 7 per cent of the total drug found in the blood at any given time.

A comparison was made of the effectiveness of 3–4, Dimethyl-5-sulfanilamido-isoxazole with that of sulfadiazine in controlling experimental infections produced in mice by Strep. hemolyticus, D. pneumoniae (Type I) Kl. pneumoniae (Type A) and H. influenzae (Type b). In mice fed with this compound or sulfadiazine for a total of 7 days in amounts adequate to produce similar concentrations of these drugs in the blood of the animals, and infected with similar doses of Strep. hemolyticus (C-203) by the intraperitoneal route after 48 hours of the drug feeding, the protective action of this drug was comparable to that of sulfadiazine, if not somewhat better. The same was true when D. pneumoniae (SVI) was the infecting organism. When Kl. pneumoniae (Type A) was employed to produce the

* These investigations were supported by grants from Abbott Laboratories, Eli Lilly and Company, Lederle Laboratories, Inc., Parke, Davis and Company, and the Upjohn Company.

infections, sulfadiazine was more effective. In infections produced in mice by the inoculation of H. influenzae (Type B) neither drug was effective in the doses employed.

CONCLUSIONS

1. The experimental acute toxicity of 3–4, Dimethyl-5-sulfamilamido-isoxazole is low.
2. The drug appears to be only partially absorbed from the gastro-intestinal tract.
3. The rate of acetylation of this compound in the tissues and body fluids seem to be low.
4. In the blood, very little of the drug enters the blood cells as approximately 93% of the compound is found in the plasma.
5. This sulfonamide derivative seems to be comparable to sulfadiazine in its ability to protect mice against Beta hemolytic streptococcal and pneumonococcal infections. It is not as effective as sulfadiazine in experimental infections in mice produced by Kl. pneumoniae. In the experiments reported in this abstract neither compound was protective against experimental infections produced by H. influenzae Type B.
6. Clinical trials with 3–4, Dimethyl-5-sulfanilamido-isoxazole would appear justifiable.

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Dr. E. K. Marshall, Jr.: When Dr. Schnitzer's paper came out a year or so ago this drug interested me very much. I think one of the most interesting things about it (Dr. Long didn't mention it) is the fact that it and its acetyl derivatives are about as soluble as sulfanilamide. It was predicted that this compound would not cause renal concretions. We have made a few studies on it. It is distributed in the dog and in the human being only in extracellular water. In the dog its apparent volume of distribution is about 25 to 30 per cent of the body weight, and in man about 20 to 25 per cent, which corresponds roughly to the extracellular water. The importance of this observation is that with a drug present only in extracellular water one would not expect it to exhibit certain toxic properties which would be exhibited by a drug in intracellular fluids. Sulfanilamide and sulfapyridine, the first sulfonamides to be used clinically, are distributed in 80 to

85 per cent of the body weight and have certain toxic characteristics which are not shared by sulfadiazine, which is distributed in 45 to 55 per cent of body weight. I would predict that this new drug will show far less toxicity than the other sulfonamides. Another advantage of this drug being distributed only in extracellular water is that with the same dose of this drug one would obtain three times as high a plasma level as you would with sulfanilamide or sulfapyridine.

Dr. Arnold R. Rich: I would like to ask Dr. Marshall, when he says toxicity does he mean hypersensitivity also? Because there, of course, the drug combines with the plasma protein in most instances.

Dr. Marshall: No, I don't think it would have any effect on that.

*In Vitro Studies of Polymyxin.** DRS. ELEANOR A. BLISS, CAROLINE A. CHANDLER and EMANUEL B. SCHOENBACH (*Department of Preventive Medicine, The Johns Hopkins University School of Medicine*).

Polymyxin is a new antibiotic agent the activity of which is restricted to gram-negative bacteria. Benedict and Langlykee (1) were the first to report that extracts of B. polymyxa inhibted bacterial growth. Quite independently Stansly and his associates (2, 3, 4) described the active principle and named it "polymyxin". Meanwhile Brownlee et al (5, 6) reported on "aerosporin" which appears to be similar but not identical with polymyxin.

The observations of other investigators regarding certain of the physicochemical properties, as well as the antibacterial action of polymyxin have been confirmed. The agent, *in vitro*, is most effective in an acid environment. It is quite stable to heat and loses but little activity in the presence of serum. The combination of heat and serum, however, is deleterious. Most strains of E. coli, Aerobacter and Friedlander's bacillus are susceptible to 0.3 microgram of polymyxin per cc., when an inoculum of about 200,000 bacilli is used. H. influenzae is equally susceptible. Pseudomonas aeruginosa required 2.5 μg./cc., while strains of Proteus and meningococci appear to be resistant *in vitro*. Attempts to produce resistance in sensitive strains have been unsuccessful. End points in titrations are clear cut and further incubation does not cause them to shift. This observation and studies of growth curves show that the drug is bactericidal in concentrations above 0.2 μg./cc. However, the addition of polymyxin at intervals after growth has started fails to result in sterilization of the cultures. This may be due to the fact that the size of the inoculum is extremely important. Large inocula of E. coli grow out in relatively high concentrations of the agent. Such cultures, freed of bacteria, are found to have lost much of their polymyxin activity, either because of destruction or adsorption of the agent. Aquaeous emulsions of soy bean lecithin also interfere with the action of polymyxin.

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* These investigations were supported by grants from Abbott Laboratories, Eli Lilly and Company, Lederle Laboratories, Inc., Parke, Davis and Company, and the Upjohn Company.

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*The Experimental Toxicology, Pharmacology, and Effectiveness of Polymyxin.** DRS. MORTON S. BRYER, EMANUEL B. SCHOENBACH, ELEANOR A. BLISS and C. EARL OTT (*Department of Preventive Medicine, The Johns Hopkins University School of Medicine*).

The acute toxicity of "polymyxin" was determined in mice by single subcutaneous injection and the L.D. 50 was 250–300 mg/kilo. Dogs survived single, rapid intravenous injections of 10 and 15 mg/kilo, while 25 mg/kilo resulted in convulsions, apnea, and death. Continuous intravenous administration at the rate of 0.25 mg/kilo per minute resulted in paralysis, apnea, and death when 35 mg/kilo had been given. Dogs tolerated 5 and 10 mg/kilo intramuscularly twice daily for 7 days. Intrathecal injection of 1 and 5 mg. was associated with no untoward reaction while 10 mg. produced transient paresis.

Ninety minutes after single intramuscular doses of 5 and 10 mg/kilo in dogs' serum levels of 2.5 and 5.0 gamma/cc. were obtained. Three and a half hours after these injections serum contained 2.5 and 1.25 gamma/cc. respectively. Levels obtained were approximately four times higher when dogs had been maintained on these doses twice daily for 7 days. Despite persistent high serum levels no polymyxin was detected in the spinal fluid. Intrathecal administration of 1, 5, and 10 mgs. resulted in spinal fluid levels of 10–500 gamma/cc. which fell to 0.3–20 gamma/cc. in 2 to 4 hours. Serum levels of 0.6–1.25 gamma/cc. were obtained following intrathecal doses of 5 and 10 mgs.

Single subcutaneous injection of 1 mg/kilo protected the majority of mice infected intraperitoneally with 1000 L.D.'s of Kl. pneumoniae A or H. influenzae B. A single initial dose was more effective than the same amount of "polymyxin" given in divided doses. Delay in treatment resulted in a reduction in the number of survivors. Polymyxin was more than five times as effective as streptomycin by weight.

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* These investigations were supported by grants from Abbott Laboratories, Eli Lilly and Company, Lederle Laboratories, Inc., Parke, Davis and Company, and the Upjohn Company.

*The Clinical Use of Polymyxin.** DRS. EMANUEL B. SCHOENBACH, MORTON S. BRYER, ELEANOR A. BLISS and PERRIN H. LONG (*Department of Preventive Medicine, The Johns Hopkins University School of Medicine*).

The clinical trial of "polymyxin" for the treatment of patients ill with infections caused by gram-negative bacteriae appeared desirable in light of the wide differential between toxicity and therapeutic activity observed in experimental animals. The inability to demonstrate the development of resistance to this antibiotic was a distinct advantage when compared to previous experience with streptomycin.

The dosage employed in these early cases varied from 3.0 to 5.0 milligrams per kilogram of body weight daily. The total daily amount was divided into eight equal parts and administered intramuscularly every 3 hours. The drug was dissolved in a phosphate buffer pH 7.6 and 40–50 milligrams in one cubic centimeter caused no local irritation or discomfort. Blood, urine and spinal fluid samples were obtained at various intervals for bioassay of polymyxin levels. Blood levels varied from 1.3 to 20 gamma per cubic milliliter on this dosage regime. The higher levels were usually not attained until the seventh to tenth day of treatment. None of the polymyxin was detected in the spinal fluid following intramuscular injection, but on one occasion a level of 5 gamma per cubic milliliter was noted 12 hours after the intrathecal administration of 2.0 milligrams of drug. Urinary excretion of polymyxin was low in the first 12 hour period but increased exponentially as therapy was continued, so that approximately 60 per cent of the total drug was detected 96 hours after administration had been begun. The concentration of polymyxin in the urine varied from 0.25 gamma to 160.0 gamma per cubic milliliter. Levels above 1.0 gamma were not attained until approximately 24 hours after therapy had been instituted.

Five patients ill with infections due to Ps. aeruginosa, Br. abortus and Kl. pneumoniae have been treated for periods of eleven to twenty-nine days. The drug was well tolerated. Among these severely ill patients, two showed transitory albuminuria and one a diffuse macular eruption. These were not attributed to polymyxin. On two occasions a transitory vasomotor reaction 10–20 minutes after an injection was noted. One patient developed febrile response on the 17th day of treatment. His temperature fell to normal when treatment was discontinued. The clinical course of these patients treated with polymyxin indicate that the antibiotic was beneficial. The results confirm previous observations on the chemotherapy of experimental infections in mice.

Dr. Harold J. White: I would like to say that the results obtained in our laboratory are in complete agreement with the findings that Dr. Bliss and Dr. Bryer have reported here tonight. We are convinced that: (1) polymyxin is practically

* These investigations were supported by grants from Abbott Laboratories, Eli Lilly and Company, Lederle Laboratories, Inc., Parke, Davis and Company, and the Upjohn Company.

specific for gram-negative bacteria; (2) it is bactericidal, and rapidly so; (3) in experimental infections, the total daily dose is more effective when given all at once than when divided into frequent doses; (4) with polymyxin, one would not expect to encounter bacterial resistance as a serious problem. There seems to be no discrepancy between our results and those just reported.

Dr. Rich: I would like to ask Dr. Schoenbach if bacillus pertussis was recovered from either of those cases which he mentioned.

Dr. Horace L. Hodes: Pertussis organisms were not recovered from either of the patients described by Doctor Schoenbach. We not infrequently fail to recover pertussis bacilli from young infants with typical whooping cough. I do not believe that there is any doubt about the diagnosis. We cannot be sure that the polymyxin was of any benefit. Our impression is that the course of the disease in the younger infant was greatly shortened. About the older child, we can draw no conclusion whatever. We have found in the laboratory that between 0.5 and 2.0 micrograms of polymyxin per cc. of media inhibits the growth of Hemophilus pertussis. Preliminary experiments indicate that polymyxin has a definite protective action against this organism in mice. Regarding the child with the pseudomonas aeruginosa (pyocyaneus) infection, I do not believe that there is any doubt but that polymyxin was of great benefit. I am quite convinced that the child would not have survived unless he had been treated with this drug.

Dr. Marshall: I would like to ask if any changes were found in the urine except in one case, the first one. I realize that we are working with a very impure mixture. Until this substance is obtained pure we must always be suspicious as to whether the pure antibiotic causes the reaction or whether it is due to the impurities present. Were there any changes in the dogs' urine, Dr. Bryer?

Dr. Morton S. Bryer: I didn't examine the urine.

Dr. Hodes: In the case of that first child, there were changes in his urine when he came into the hospital.

Dr. Emanuel B. Schoenbach: All these patients have been acutely and seriously ill. This child had 3-plus albuminuria, 104° fever and pyuria, which disappeared while on therapy. It is a question whether polymyxin caused the albuminuria or whether it was just due to the febrile response.

Dr. Perrin H. Long: Dr. Schoenbach said that the dosage of polymyxin was arbitrary. It was and was put upon Dr. Schoenbach and Dr. Bryer by myself because, in introducing a new antibiotic, I wanted to err as much as possible on the side of safety to the patient. In the experimental animals, it is interesting that this antibiotic has shown greater acute toxicity than any other antibiotic with which we have worked. Small and divided doses are safer to use in the early part

of such studies until we know more about its toxicity in human beings. As a result of our experience to date, I think that in the near future we will give the antibiotic less frequently, and will give half the daily total as the initial dose, and then a quarter of the total daily dose 8 and 16 hours later, and then a third of the daily dose at 8 hourly intervals on subsequent days. We will see whether this dosage schedule is more effective in bringing the disease under control early in the course of treatment. It is difficult, when you are fishing around in the dark, to hit upon exactly the right dosage schedule, and, as I said, you always want to err on the side of safety in working with any new antibiotic.

Dr. Rich: Were there any pathological studies made with animals?

Dr. Long: No, no pathological studies were made on the animals that died of acute toxicity. There was no real evidence of chronic toxicity as far as we went. There were no pathological studies made on the mice which died, or on the dogs. We would like to have some one make the studies, especially on those animals that died acutely in convulsions. We would like to know what the drug does to the central nervous system. The organs are preserved in formalin.

Dr. A. Murray Fisher: I was interested in Dr. Bliss' report of the apparent development of resistance of the organisms during their growth with low concentrations of polymyxin. I wonder if she tried spinning the cultures down to separate them from the media, regrowing them, and retesting them with polymyxin.

Dr. Eleanor A. Bliss: What we did was to take the bacteria which had grown in the presence of polymyxin, large inocula of E. coli for instance, which had grown out, and used that, diluting it down to usual size, 200,000 per cc. We found it was not resistant. When we centrifuged, we were trying to see whether the polymyxin that was left in the tube was as strong as what was there in the beginning. The cultures have all been grown between testing for resistance and at the time they were in the tube.

Dr. Fisher: I mean, when you spun the cultures down, did you separate the bacteria from the media and test them for resistance?

Dr. Bliss: No, we did not spin the cultures down and test them for resistance. We used them as broth cultures and just diluted them.

Dr. Long: Another thing which Dr. Schoenbach or Dr. Bryer may have spoken about tonight was rather puzzling. As you noted on one of those charts, meningococci on plate cultures were quite resistant to polymyxin, even to 20 to 30 micrograms of the antibiotic per cubic centimeter. However, when the antibiotic was injected in mice infected by using mucin and meningococci we found that polymyxin in a single dose cured 100 per cent of the mice. Now, there is a difference between in vitro and in vivo findings. We are still working to try to explain the difference in reaction.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal)

Emotional Maturity. By LEON J. SAUL. 338 pp. $5.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1947.

In this book by Dr. Saul, Associate Professor of Psychiatry at the Temple University School of Medicine, the focus of interest throughout is clinical and therapeutic. As indicated by the title, Dr. Saul employs a framework of reference which includes attention not only to dynamic pathological patterns but also to the biological process of emotional growth and to faults in this process as a source of adult maladjustment.

The material of the book is presented in four parts. To the present reviewer, the discussion in Part I, the Achievement of Maturity, and Part II, Emotional Forces in the Development of the Personality, seemed most valuable, and alone would have justified the publication of this book. Here the author formulates his concept of emotional maturity and of the maturation process. Some of the central features which he depicts are the shifts which the individual is required to make in his functioning in relationships with others in the course of his maturation: the shift from the childhood pattern of dependence, freedom from responsibilities and being protected to the adult capacity for carrying responsibility, being depended on and providing protection; the shift from primarily *getting* in relationships with others to enjoying *giving*; and the shift from egotism, competitiveness and inferiority feelings to a kindly and cooperative adjustment to others, with enjoyment of one's own productive activity. The persistence of certain childhood patterns into chronological adulthood is described as leaving the individual with vulnerable emotional points—the "emotional Achilles heel." The presence of these vulnerable emotional points makes the individual sensitive to specific situational stresses while leaving him resistant to other severe stresses which would be disturbing to another individual with another set of vulnerable points. The author makes the point that reservoirs of childhood needs remain even in adults who have attained a high degree of emotional maturity and that these needs are filled in play and recreational outlets.

Part III, The Nature of Neurosis, is almost a book within a book. It is based on the author's war-time clinical experience with navy psychiatric casualties and is rich in clinical material. This case material is aptly selected and is presented with clarity and enviable brevity. It serves as a basis for illustrating the concept of specific emotional vulnerability and for a consideration of the meaning of various emotional responses such as fear, hostility, flight, fight, etc. To Dr. Saul the term neurosis implies "a failure of adaptation and a disturbance of the patient's emotional development." The nature of neurosis is "reaction to stress upon vulnerable

points and fight-flight reactions along the lines of childhood patterns." With regard to therapy the author states that, in contrast to the results produced by rest and temporary relief from duty, "circumscribed but carefully focused psychotherapy, aimed at the specific source of the patient's reactions, produced marked results after only one or two interviews."

Part IV, The Dynamics of Personality, reads rather like lectures to medical students. It is a brief section and neither adds nor detracts from the book as a whole.

There is a reference list of 112 titles, and an index.

B. B.

Gynecological and Obstetrical Urology. 2nd Edition. By HOUSTON S. EVERETT. Illus. 539 pp. $6.00. *The Williams & Wilkins Company, Baltimore, Maryland,* 1947.

Dr. Everett has made a number of timely changes and additions in the second addition of his textbook. A section on indirect, or "water", cystoscopy has been added since most urologists employ this method rather than the direct, or Kelly method. Indications for use of the two methods are given, and the common indirect cystoscopic instruments are illustrated and described. Other additions to the text include a discussion of the use of penicillin in urinary tract infections and a description of the Aldridge operation for urinary incontinence, with illustrations demonstrating the operative technique. The chapter on "Neoplastic Disease of the Bladder" has been completely rewritten, stress being laid on the importance of *infiltration* rather than the gross or microscopic appearance of the tumor alone. Dr. Everett emphasizes that all these factors, together with the characteristics of the tumor on pelvic examination, must be considered before the type of treatment is determined in any particular case. This textbook has always been a very complete one, and the present edition brings it up to date. The style is clear and the viewpoint sound. Dr. Everett is to be congratulated on producing an excellent book. In the writer's opinion, it is the best and most up to date work of its kind in the literature of today.

C. B. B.

Jaundice, Its Pathogenesis and Differential Diagnosis. By ELI RODIN MOVITT. Illus. 261 pp. $6.50. *Oxford University Press, New York, New York,* 1947.

The difficulties which the clinician meets in the differential diagnosis of jaundice are reflected in the frequency with which the subject is reviewed in the medical literature. Movitt has attempted "to aid the practicing physician" in this task. He reviews in orderly fashion the anatomy and physiology of the liver, the pathogenesis of jaundice, diagnostic procedures, and the differential diagnosis of the individual syndromes associated with jaundice. Interspersed throughout the text are tables summarizing the points which Movitt believes require emphasis.

The arrangement of subjects is clear and logical. Certain features, however, tend to limit the utility of this book. The textual material is presented didacti-

cally and usually without reference to those authors upon whose shoulders Movitt seems to have leaned heavily. The bibliography at the end of each chapter is not helpful, since it is not possible to tell to which subject any given article refers.

There are a number of textual and bibliographic inaccuracies as well. For example, prothrombin is usually believed to be associated with the globulin rather than the albumin fraction of human plasma. The reviewer, too, might take issue with some of the author's concepts, but, in a controversial field, differences of opinion are surely healthy. Thus, one might question the separation of acute infectious hepatitis and catarrhal jaundice. Again, in our hands, the determination of serum alkaline phosphatase has been one of the most satisfying of differential diagnostic procedures. The format and printing of this volume are pleasing and attractive. None of the deficiencies of the book are beyond repair in a future edition.

O. D. R.

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Catalogue of Medical Films. Compiled by THE ROYAL SOCIETY OF MEDICINE AND THE SCIENTIFIC FILM ASSOCIATION. 127 pp. 7s.6d. *Aslib, London, W.C.1,* 1948.

Epithelia of Woman's Reproductive Organs, The. By GEORGE N. PAPANICOLAOU, HERBERT F. TRAUT, AND ANDREW A. MARCHETTI. Illus. 53 pp. $10.00. *The Commonwealth Fund, New York 22, New York,* 1948.

Headache, and other Head Pain. By HAROLD G. WOLFF. Illus. 642 pp. $12.00. *Oxford University Press, New York, New York,* 1948.

Integrative Action of the Nervous System, The. 2nd edition. By SIR CHARLES SHERRINGTON. Illus. 433 pp. $6.00. *Yale University Press, New Haven, Connecticut,* 1948.

Introduction to Human Physiology. By WILLIAM D. ZOETHOUT. Illus. 424 pp. $4.00. *C. V. Mosby Company, St. Louis, Missouri,* 1948.

Pathology of Tumours. By RUPERT A. WILLIS. Illus. 992 pp. $20.00. *C. V. Mosby Company, St. Louis, Missouri,* 1948.

Psychobiology and Psychiatry. 2nd edition. By WENDELL MUNCIE. Illus. 620 pp. $9.00. *C. V. Mosby Company, St. Louis, Missouri,* 1948.

Symposium on Medicolegal Problems. Edited by SAMUEL A. LEVINSON. 255 pp. $5.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1948.

Textbook of Gynecology. 3rd edition. By EMIL NOVAK. Illus. 742 pp. $8.00. *The Williams & Wilkins Company, Baltimore, Maryland,* 1948.

Topics in Physical Chemistry. By W. MANSFIELD CLARK. Illus. 738 pp. $10.00. *The Williams & Wilkins Company, Baltimore, Maryland,* 1948.

Treatment by Diet. 5th edition. By CLIFFORD J. BARBORKA. Illus. 784 pp. $10.00. *J. B. Lippincott Company, Philadelphia, Pennsylvania,* 1948.

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